Intent to Treat 2	2 (6.3%)	Λ	2
Intent-to-Treat 2	2 (0.3%)	U	1 2 1

Patients may be counted more than once. Reviewer's table

Belgium - Center 4 Results-

	Enoxaparin (number of	Desirudin (number of	Total (number
	patients)_	patients)	of patients)
Randomized	27	27	54
Prophylaxis period completed	26	25	51
Discontinued prematurely	1	2	3
Other reason	1 (WC)	2 (WC)	3
Efficacy Analysis			
Per-protocol	22 (81.5%)	24 (88.9%)	46 (85.2%)
Intent-to-Treat 1	22 (81.5%)	24 (88.9%)	46 (85.2%)
Intent-to-Treat 2	27 (100%)	27 (100%)	54
Excluded from PP , ITT*	5	3	8
Inadequate central reading	1	0	1
Missing	1 (pt # 5116)	0	1
No phlebography	3	3	6
Efficacy Results			
Per-protocol	3 (13.6%)	0	3
Intent-to-Treat 1	3 (13.6%)	0	3
Intent-to-Treat 2	3 (11.1%)	0	3

Patients may be counted more than once. Reviewer's table

Denmark - Center 1 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Tota! (number of patients)
Randomized	20	21	41
Prophylaxis period completed	20	17	37
Discontinued prematurely	0	4	4
Adverse Event	0	1	1
Other reason	0	3 (AP, NC, WC)	3
Treated no operation	0	2	2
Efficacy Analysis			
Per-protocol	19 (95%)	15 (71.4%)	34 (82.9%)
Intent-to-Treat 1	19 (95%)	15 (71.4%)	34 (82.9%)
Intent-to-Treat 2	_ 20	21	41
Excluded from PP and ITT*	1	6	5
Inadequate central reading	1	0	1
Missing	0	2 (pt # 9040, 9098)	2
No operation	0	2	2
No phlebography	0	4	4
Efficacy Results			
Per-protocol .	1 (5.3%)	0	1
Intent-to-Treat 1	1 (5.3%)	0	1
Intent-to-Treat 2	1 (5%)	0	1

*Patients may be counted more than once.

Reviewer's table

Denmark - Center 2 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	27	25	52
Prophylaxis period completed	21	21	42
Discontinued prematurely	6	4	10
Adverse Event	1	0	1
Other reason	5 (1 AP, 2 PX, 2 WC)	4 (2 AP, 1 PX, 1 WC)	9
Treated, but no operation	3 (2 PX, 1 WC)	2 (AP)	5
Efficacy Analysis			
Per-protocol	19 (70.4%)	19 (76%)	38 (73.1%)
Intent-to-Treat 1	19 (70.4%)	19 (76%)	38 (73.1%)
Intent-to-Treat 2	27	25	54
Excluded from PP , ITT*	8	6	14
Inadequate central reading	1	2	3
No operation performed	3	2	5
No phlebography	7	4	11

Efficacy Results			
Per-protocol	0	2 (10 5%)	2
Intent-to-Treat 1	0	2 (10.5%)	2
Intent-to-Treat 2	0	2 (8%)	2

Patients may be counted more than once. Reviewer's table

Denmark - Center 3 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	14	15	29
Prophylaxis period completed	13	13	26
Discontinued prematurely	1	2	3
Death	0	0	0
Adverse Event	0	C	0
Other reason	1 (WC)	2 (PX, WC)	3
Treated, but no operation	0	0	0
Efficacy Analysis			
Per-protocol	11 (78.6%)	12 (80%)	22 (75.9%)
Intent-to-Treat 1	11 (78.6%)	12 (80%)	23
Intent-to-Treat 2	14	15	29
Excluded from PP , ITT	3	3	6
Inadequate central reading	2		3
No phlebography	1	2	3
Efficacy Results			
Per-protocol	0	0	0
Intent-to-Treat 1	0	0	0
Intent-to-Treat 2	0	0	0

Patients may be counted more than once.

Reviewer's table

Denmark - Center 4 Results-

	Enoxaparin (number of	Desirudin (number of	Total (number of
	patients)	patients)	patients)
Randomized	29	28	57
Prophylaxis period completed	23	26	49 .
Discontinued prematurely	6	2	8
Death	0	0 /	0
Adverse Event	2	1	3
Other reason	4 (2 PX, 2 WC)	1 (WC)	5
Treated, but no operation	3 (AE, 2 PX)	0	3
Efficacy Analysis			
Per-protocol	20 (69%)	22 (78.6%)	42 (89.4%)
Intent-to-Treat 1	20 (69%)	22 (78.6%)	42 (89.4%)
Intent-to-Treat 2	29	28	57
Excluded from PP , ITT*	9	6	15
Missing	1 (pt # 9132)	1 (pt # 9072)	2
No operation	3	0	3
No phlebography	8	5	13
Efficacy Results			
Per-protocol	0	0	0
Intent-to-Treat 1	0	0	0
Intent-to-Treat 2	0	0	0

Patients may be counted more than once. Reviewer's table

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France - Center 1 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	23	26	49
Prophylaxis period completed	23	26	49
Discontinued prematurely	0	0	0
Efficacy Analysis			
Per-protocol	20 (87%)	21 (80.8%)	41 (83.7%)
Intent-to-Treat 1	20 (87%)	22 (84.7%)	42
Intent-to-Treat 2	23	26	49
Excluded from PP and ITT*	3	4	7
Inadequate central reading	1	0	1

Missing	1 (pt # 7011)	4 (pt # 7008, 7010, 7017, 7114)	5
No phlebography	1	0	1
Excluded from PP	0	1	1
Phlebography performed at wrong time	0	1	1
Efficacy Results			
Per-protocol	2 (10%)	2 (9.5%)	4
Intent-to-Treat 1	2 (10%)	2 (9.1%)	4
Intent-to-Treat 2	2 (8.7%)	2 (7.7%)	4

Patients may be counted more than once. Reviewer's table

France - Center 2 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	8	11	19
Prophylaxis period completed	8	11	19
Discontinued prematurely	0	0	0
Efficacy Analysis			
Per-protocol	7 (87.5%)	11	18 (94.7%)
Intent-to-Treat 1	7.(87.5%)	11	18 (94.7%)
Intent-to-Treat 2	8	11	19
Excluded from PP, ITT	1	0	1
Missing	1 (pt # 7026)	0	1
Efficacy Results			
Per-protocol	2 (28.6%)	1 (9.1%)	3
Intent-to-Treat 1	2 (28.6%)	1 (9.1%)	3
Intent-to-Treat 2	2 (25%)	1 (9.1%)	3

Patients may be counted more than once. Reviewer's table

France - Center 3 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	15	16	31
Prophylaxis period completed	13	13	26
Discontinued prematurely	2	3	5
Death	0.	0	0
Adverse Event	- 1	1	2
Other reason	1 (PX)	2 (AP, PX)	3
Treated, but no operation	1 (AE)	1 (PX)	2
Efficacy Analysis			
Per-protocol	11 (73.3%)	13 (81.3%)	24 (77.4%)
Intent-to-Treat 1	13 (86.7%)	15 (93.8%)	28 (90.3%)
Intent-to-Treat 2	15	16	
Excluded from PP and ITT*	2	3	5
No operation	1	1	2
No phlebography	2	2	4
Excluded from PP* only	2	0	2
Concomitant medication not allowed	2	0	2
Efficacy Results			
Per-protocol	1 (9.1%)	2 (15.4%)	3
Intent-to-Treat 1	1 (7.7%)	2 (13.3%)	3
Intent-to-Treat 2	1 (6.7%)	2 (12.5%)	3

Patients may be counted more than once. Reviewer's table

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France - Center 4 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	25	26	51
Prophylaxis period completed	24	25	49
Discontinued prematurely	1	1	2
Death	0	0	0
Adverse Event	0	1 (PE)	1
Other reason	1 (AP)	0	1
Treated, but no operation	0	0	0
Efficacy Analysis			

Per-protocol	7 (28%)	10 (38.5%)	17 (33.3%)
Intent-to-Treat 1	7 (28%)	11 (42.3%)	18 (35.3%)
Intent-to-Treat 2	25	26	51
Excluded from PP , ITT*	18	16	34 (66.7%)
Concomitant medication not	0	1	1
allowed			
inadequate central reading	0	3	3
Missing	15 (pt # 7083, 7084, 7086, 7087, 7089, 7094, 7095, 7149, 7150, 7151, 7157, 7163, 7164, 7165, 7168)	11 (pt # 7075, 7079. 7085, 7088, 7090, 7091, 7093, 7145, 7158, 7159, 7160)	26 (51%)
No phlebography	3	2	5
Excluded from PP*	0	1	1
Concomitant medication not allowed	0	1	1
Efficacy Results			
Per-protocol	1 (14.3%)	4 (40%)	5
intent-to-Treat 1	1 (14.3%)	4 (36.4%)	5
Intent-to-Treat 2	1 (4%)	4 (15.4%)	5

Patients may be counted more than once. Reviewer's table

Germany - Center 1 Results-

-	Enoxaparin (number	Desirudin (number of	Total (number
	of patients)	patients)	of patients)
Randomized	66	66	132
Prophylaxis period completed	63	65	128
Discontinued prematurely	3	1	4
Adverse Event	3	1	4
Treated, but no operation	0	1 (AE)	1
Efficacy Analysis			
Per-protocol	46 (69.7%)	54 (81.1%)	100 (75.5%)
Intent-to-Treat 1	47 (71.2%)	56 (84.8%)	103 (78%)
Intent-to-Treat 2	66	66	132
Excluded from PP and ITT*	19	10	29 (22° ₅)
Concomitant medication, not allowed	1	2	3
Inadequate central reading	5	1	6
Missing	8 (pt # 6065, 6082,	4 (pt # 6063, 6072,	12
	6111, 6114, 6127,	⁷ 6151, 9952)	
-	6150, 9964, 9967)		<u> </u>
No operation	0	1	1
No phlebography	6	4	10
Excluded from PP* only	1	2	3
Concomitant medication, not allowed	1	2	3
Efficacy Results			1
Per-protocol	5 (10.9%)	2 (3.7%)	7
Intent-to-Treat 1	5 (10.6%)	2 (3.6%)	7
Intent-to-Treat 2	5 (7.6%)	2 (1.5%)	7

Patients may be counted more than once. Reviewer's table

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Germany - Center 2 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	44	44	88
Prophylaxis period completed	43	43	86
Discontinued prematurely	1	1	2
Other reason	1 (WC)	1 (WC)	2
Efficacy Analysis			
Per-protocoi	34 (77.3%)	30 (68.2%)	64 (72.7%)
Intent-to-Treat 1	34 (77.3%)	31 (70.5%)	65 (73.9%)
Intent-to-Treat 2	44	44	88
Excluded from PP and ITT	10	13	23 (26.1%)
Inadequate central reading	6	10	16
No phlebography	4	3	7
Excluded from PP only	0	1	1
Concomitant medication not allowed	0	1	1

Efficacy Results			
Per-protocol	2 (5.9%)	3 (10%)	5
Intent-to-Treat 1	2 (5.9%)	3 (9.7%)	5
Intent-to-Treat 2	2 (4.5%)	3 (6.8%)	5

Patients may be counted more than once. Reviewer's table

Italy - Center 1 Results-

,	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	31	32	63
Prophylaxis period completed	29	29	58
Discontinued prematurely	2	3	5
Adverse Event	2	2	4
Other reason ·	0	1 (PX)	1
Efficacy Analysis			
Per-protocol Per-protocol	19 (61.3%)	22 (68.8%)	43 (68.3%)
Intent-to-Treat 1	21 (67.8%)	24 (75%)	45 (71.4%)
Intent-to-Treat 2	31	32	63
Excluded from PP and ITT	. 10	8	18 (28.6%)
Inadequate central reading	2	2	4
Missing	1 (pt # 7677)	2 (pt # 7502, 7565)	3
No phlebography	7	4	11
Phlebography performed at wrong time	0	1	1
Excluded, from PP	2	2	4
No phlebography	1	0	1
Phlebography performed at the wrong time		2	3
Efficacy Results			
Per-protocol Per-protocol	2 (10.5%)	1 (4.5%)	3
Intent-to-Treat 1	2 (9.5%)	1 (4.2%)	3
Intent-to-Treat 2	2 (6.5%)	1 (3.1%)	3

^{*} Patients may be counted more than once. Reviewer's table

Italy - Center 2 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	34	36	70
Prophylaxis period completed	33	35	68
Discontinued prematurely	1	1	2
Adverse Event	1	1	2
Efficacy Analysis			
Per-protocol	28 (82.4%)	29 (80.6%)	57 (81.4%)
Intent-to-Treat 1	28 (82.4%)	29 (80.6%)	57 (81.4%)
Intent-to-Treat 2	34	36	70
Excluded from PP and ITT	6	7	13
Inadequate central reading	1	0	1
Missing	1 (pt # 7542)	0	1
No phlebography	4	7	11
Efficacy Results			
Per-protocol	2 (7.1%)	1 (3.4%)	3
Intent-to-Treat 1	2 (7.1%)	1 (3.4%)	3
Intent-to-Treat 2	2 (5.9%)	1 (2.8%)	3

^{*} Patients may be counted more than once. Reviewer's table

Italy - Center 3 Results-

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	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	35	35	70
Prophylaxis period completed	34	34	68
Discontinued prematurely	1	1	1
Adverse Event	1	1	1
Efficacy Analysis			
Per-protocol	30 (85.7%)	25 (71.4%)	55 (78.6%)
Intent-to-Treat 1	30 (85.7%)	25 (71.4%)	55 (78.6%)

Intent-to-Treat 2	35	35	70
Excluded from PP and ITT	5	10	15
Inadequate central reading	2	5	7
Missing	2 (pt # 7256, 7616)	0	2
No phlebography	1	5	6
Efficacy Results			
Per-protocol	4 (13.3%)	2 (8%)	6
Intent-to-Treat 1	4 (13.3%)	2 (8%)	6 ,
Intent-to-Treat 2	4 (11.4%)	2 (5.7%)	6

^{*} Patients may be counted more than once. Reviewer's table

Netherlands 1 - Center 1 Results - +

	Enoxaparin (number of	Desirudin (number of	Total (number of
	patients)	patients)	patients)
Randomized	25	25	50
Prophylaxis period completed	24	23	47
Discontinued prematurely	1	2	3
Adverse Event	0	2	2
Other reason	1 (AP)	0	1
Efficacy Analysis			
Per-protocol	16 (64%)	16 (64%)	32 (64%)
Intent-to-Treat 1	17 (68%)	17 (68%)	34 (68%)
Intent-to-Treat 2	25	25	50
Excluded from PP and ITT	8	8	16 (32%)
Inadequate central reading	1	5	6
Missing	1 (pt # 8042)	0	1
No phlebography	6	3	9 .
Excluded from PP only	1	1	2
Concomitant medication not allowed	1	1	2
Efficacy Results			
Per-protocol	2 (12.5%)	1 (6.3%)	3
Intent-to-Treat 1	2 (11.8%)	1 (5.9%)	3
Intent-to-Treat 2	2 (8%)	1 (4%)	3

^{*} Patients may be counted more than once. Reviewer's table

Netherlands - Center 2 Results-

	Enoxaparin	Desirudin	Total (number of
•	(number of	(number of	patients)
	patients)	patients)	
Randomized	41	42	83
Prophylaxis period completed	40	40	80
Discontinued prematurely	1	2	3
Adverse Event	1	2	3
Efficacy Analysis			
Per-protocol	16 (39%)	16 (38.1%)	32 (38.6%)
Intent-to-Treat 1	17 (41.5%)	17 (40.5%)	34 (41%)
Intent-to-Treat 2	41	42	83
Excluded from PP and ITT*	24	25	49 (59%)
Concomitant medication, not allowed	2	0	2
Inadequate central reading	4	9	13
Missing	1 (pt # 8115)	2 (pt # 8112, 8180)	3
No phlebography	19	13	32
Phlebography performed at the wrong time	0	1	1
Excluded from PP only	1	1	2
Concomitant medication, not allowed	1	0	1
Phlebography performed at the wrong time	0	1	1
Efficacy Results			
Per-protocol	1 (6.3%)	1 (6.3%)	2
Intent-to-Treat 1	1 (5.9%)	1 (5.9%)	2
Intent-to-Treat 2	1 (2.4%)	1 (2.4%)	2

^{*} Patients may be counted more than once. Reviewer's table

Netherlands – Center 3 Results–	_	.		
	.	Enoxaparin (number of	Desirudin (number	Total (number
		patients)	of patients)	of patients)

Randomized	36	35	71
Prophylaxis period completed	28	31	59
Discontinued prematurely	8	4	12
Adverse Event	2	2	4
Other reason	6 (2 AP, 1 PX, 2 WC, 1 NC)	2 (WC)	8
Efficacy Analysis			
Per-protocol	12 (33.3%)	18 (51.4%)	30 (42.3%)
Intent-to-Treat 1	15 (41.7%)	19 (54.3%)	34 (47.9%)
Intent-to-Treat 2	36	35	71
Excluded from PP , ITT*	21	16	37 (52.1%)
Concomitant medication not allowed	1	0	1
Inadequate central reading	7	7	14
Missing	0	2 (pt # 8144, 8619)	2
No phlebography	14	7	21
Phlebography performed at the wrong time	0	1	1
Excluded, from PP*	3	1	4
Concomitant medication not allowed	0	1	1
Phlebography performed at the wrong time	3	1	4
Efficacy Results			
Per-protocol	1 (8.3%)	0	1
Intent-to-Treat 1	1 (6.7%)	0	1
Intent-to-Treat 2	1 (2.8%)	0	1

^{*} Patients may be counted more than once. Reviewer's table

Spain - Center 1 Results-

	Enoxaparin (number of	Desirudin (number of	Total (number of patients)
	patients)	patients)	or patients)
Randomized	21	20	41
Prophylaxis period completed	19	17	36
Discontinued prematurely	2	3	5
Death	0	0	0
Adverse Event	1 (DVT)	2	3
Other reason	1 (PX)	1 (AP)	2
Efficacy Analysis			
Per-protocol	12 (57.1%)	11 (55%)	23 (56.1%)
Intent-to-Treat 1	12 (57.1%)	12 (60%)	24 (58.5%)
Intent-to-Treat 2	21	20	41
Excluded from PP, ITT*	9	8	17
Concomitant medication not allowed	0	1	1
Inadequate central reading	5	6	11
No phlebography	4	2	6
Phlebography performed at the wrong time	1	0	1
Excluded, from PP	0	1	1
Phlebography performed at the wrong time	0	1	11
Efficacy Results			
Per-protocol	0	2 (18.2%)	2
Intent-to-Treat 1	0	2 (16.7%)	2
Intent-to-Treat 2	0	2 (10%)	2

^{*}Patients may be counted more than once. Reviewer's table

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Spain - Center 2 Results- '

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	30	29	59
Prophylaxis period completed	28	24	52
Discontinued prematurely	2	5	7
Death	0	1	1
Adverse Event	2	1	3
Other reason	, 0	3 (PX)	3
Treated, but no operation	0	4 (3 PX, 1 AE)	4
Efficacy Analysis			
Per-protocol	22 (73.3%)	16 (55.2%)	38
Intent-to-Treat 1	23 (76.7%)	16 (55.2%)	39
Intent-to-Treat 2	30	29	59
Excluded from PP and ITT*	7	13	20

Inadequate central reading	3	2	5
Missing	2 (pt # 6629, 6661)	5 (pt # 6594, 6602, 6612, 6628, 6635)	7
No operation	0	4	4
No phlebography	2.	6	8
Excluded from PP* only	1	0	1
Concomitant medication, not allowed	1	0	1
Efficacy Results			
Per-protocol	3 (14.4%)	1 (6.3%)	4
Intent-to-Treat 1	3 (13%)	1 (6.3%)	4
Intent-to-Treat 2	3 (10%)	1 (3.4%)	4

^{*} Patients may be counted more than once. Reviewer's table

Sweden - Center 1 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	52	53	105
Prophylaxis period completed	49	47	96
Discontinued prematurely	. 3	6	9
Adverse Event	0	1 (PE)	11
Other reason	3 (2 PX, 1 WC)	5 (2 AP, 2 PX, 1 WC)	8
Treated, but no operation	0	3 (2 AP, 1 AE)	3
Efficacy Analysis			
Per-protocol	45 (86.5%)	42 (79.2%)	87 (82.9%)
Intent-to-Treat 1	45 (86.5%)	42 (79.2%)	87 (82.9%)
Intent-to-Treat 2	52	53	105
Excluded from PP , ITT	7	11	18
Concomitant medication not allowed	1	0	1
Inadequate central reading	2	4	6
No operation	0	3	3
No phlebography	5	7	12
Phlebography performed at the wrong time	0	1	1
Efficacy Results			t
Per-protocol	5 (11.1%)	2 (4.8%)	7
Intent-to-Treat 1	5 (11.1%)	2 (4.8%)	7
Intent-to-Treat 2	5 (11.1%)	2 (1.9%)	7

^{*} Patients may be counted more than once.
Reviewer's table

Sweden - Center 2 Results-

	Enoxaparin (number	Desirudin (number of	Total (number
	of patients)	patients)	of patients)
Randomized	54	53	107
Prophylaxis period completed	54	51	105
Discontinued prematurely	0	2	2
Adverse Event	0	0	0
Other reason	0	2 (PX)	2
Efficacy Analysis	1		
Per-protocol	42 (77.8%)	44 (83%)	86 (80.4%)
Intent-to-Treat 1	42 (77.8%)	44 (83%)	86 (80.4%)
Intent-to-Treat 2	54	53	107
Excluded from PP , ITT	12	9	21
Concomitant medication not allowed	0	1	1
Inadequate central reading	9	5	14
Missing	0	1 (pt # 9693)	1
No phlebography	3	3	6
Efficacy Results			
Per-protocol	2 (4.8%)	1 (2.3%)	3
Intent-to-Treat 1	2 (4.8%)	1 (2.3%)	3
Intent-to-Treat 2	2 (3.7%)	1 (1.9%)	3

^{*} Patients may be counted more than once. Reviewer's table

Sweden – Center 3 Results–			
	Enovanarin (number	Designed in Injumber of	Total (num

	of patients)	patients)	of patients)
Randomized	47	46	93
Prophylaxis period completed	42	43	85
Discontinued prematurely	5	3	8
Death	0	0	0
Adverse Event	0	0	0
Other reason	5 (4 PX, 1 WC)	3 (AP, 2 PX)	8
Treated, but no operation	3 (2 AP, 1 WC)	1 (AP)	4
Efficacy Analysis			
Per-protocol	33 (70.2%)	32 (69.6%)	65 (69.9%)
Intent-to-Treat 1	33 (70.2%)	32 (69.6%)	65 (69.9%)
Intent-to-Treat 2	47	46	93
Excluded from PP, ITT	14	14	28
Inadequate central reading	6	8	14
Missing	0	3 (pt # 9789, 9805, 9807)	3
No operation	3	1	4
No phiebography	7	3	10
Phlebography performed at wrong time	0	1	1
Efficacy Results			
Per-protocol	2 (6.1%)	0	2
Intent-to-Treat 1	2 (6.1%)	0	2
Intent-to-Treat 2	2 (4.3%)	0	2

^{*} Patients may be counted more than once. Reviewer's table

Sweden - Center 4 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	41	41	82
Prophylaxis period completed	38	36	74
Discontinued prematurely	3	5	8
Adverse Event	1 (DVT)	2	3
Other reason	2 (PX)	3 (PX, 2 WC)	5
Treated, but no operation	1 (PX)	0	1
Efficacy Analysis			
Per-protocol	30 (73.2%)	28 (68.3%)	58 (70.7%)
Intent-to-Treat 1	31 (75.6%)	28 (68.3%)	59 (72%)
Intent-to-Treat 2	41	41	82
Excluded from PP and ITT*	10	13	23
Inadequate central reading	2	4	6
Missing	1 (pt # 9866)	0	1
No operation	1	0	1
No phlebography	7	9	16
Phlebography performed at the wrong time	0	1	1
Excluded, from PP	1	0	1
Phlebography performed at the wrong time	1	0	1
Efficacy Results			
Per-protocol	2 (6.7%)	2 (7.1%)	4
Intent-to-Treat 1	2 (6.7%)	2 (7.1%)	4
Intent-to-Treat 2	2 (4.9%)	2 (7.1%)	4

^{*} Patients may be counted more than once. Reviewer's table

Switzerland - Center 1 Results-

	Enoxaparin (number of	Desirudin (number of	Total (number of
	patients)	patients)	patients)
Randomized	27	27	54
Prophylaxis period completed	26	27	53
Discontinued prematurely	1	0	1
Adverse Event	1	0	1
Efficacy Analysis			
Per-protocol	24 (88.9%)	25 (92.6%)	49 (90.7%)
Intent-to-Treat 1	25 (92.6%)	25 (92.6%)	50 (92.6%)

Intent-to-Treat 2	27 (100%)	27 (100%)	54
Excluded from PP , ITT*	2	2	4
Inadequate central reading	2	1	3
Missing	0	1 (pl #5525)	1
Excluded, from PP*	1	0	1
Phlebography performed at the	1	0	1
wrong time			
Efficacy Results			
Per-protocol	2 (8.3%)	2 (8%)	4
Intent-to-Treat 1	2 (8%)	2 (8%)	4
Intent-to-Treat 2	2 (7.4%)	2 (7.4%)	4

Patients may be counted more than once.

Reviewer's table

Switzerland - Center 2 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	27	27	54
Prophylaxis period completed	26	25	52
Discontinued prematurely	1	2	3
Adverse Event	1 .	1	2
Other reason	0	1 (WC)	1
Efficacy Analysis			
Per-protocol	20 (74.1%)	21 (77.8%)	41 (75.9%)
Intent-to-Treat 1	21 (77.8%)	21 (77.8%)	42 (77.8%)
Intent-to-Treat 2	27 (100%)	27 (100%)	54
Excluded from PP and ITT*	6	6	12
Inadequate central reading	3	4	7
Missing	1 (pt # 5539)	0	1
No phiebography	2	2	4
Phlebography performed at the wrong time	1	0	1
Excluded from PP* only	1	0	1
Phlebography performed at the wrong time	1	0	1
Efficacy Results			
Per-protocol	1 (5%)	2 (9.5%)	3
Intent-to-Treat 1	1 (4.8%)	2 (9 5%)	3
Intent-to-Treat 2	1 (3.7%)	2 (7.4%),	3

Patients may be counted more than once. Reviewer's table

Switzerland - Center 3 Results-

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	9	8	17
Prophylaxis period completed	7	5	12
Discontinued prematurely	2	3	5
Adverse Event	1	1	2
Other reason	1 (NC)	2 (AP)	3
Treated, but no operation	1 (AP)	0	1
Efficacy Analysis			
Per-protocol	7 (77.8%)	3 (37.5%)	10 (58.8 %)
Intent-to-Treat 1	7 (77.8%)	4 (50%)	11 (64.7%)
Intent-to-Treat 2	9 (100%)	8 (100 %)	17 (100%)
Excluded from PP and ITT*	2	4	6
No operation	0	1	1
No phiebography	2	4	6
Excluded from PP only	0	1	1
Phlebography performed at	0	1	1
the wrong time		l	
Efficacy Results			
Per-protocol	1 (14.3%)	0	1
Intent-to-Treat 1	1 (14.3%)	0	1
Intent-to-Treat 2	1 (11.1%)	0	1

* Patients may be counted more than once.

Reviewer's table

	Enoxaparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	1	2	3
Prophylaxis period completed	0	1	1 .
Discontinued prematurely	0	1	1
Other reason	0	1 (AP)	1
Efficacy Analysis			
Per-protocol	0 (0%)	1 (50%)	1 (33.3%)
Intent-to-Treat 1	1 (100%)	1 (50%)	2 (66.7%)
Intent-to-Treat 2	1 (100%)	2 (100%)	3
Excluded from PP and ITT*	0	1	1
Concomitant medication not allowed	0	1	1 -
No phlebography	0	1	1
Excluded from PP only	1	0	1
Concomitant medication not allowed	1	Ö	1
Efficacy Results			
Per-protocol	. 0	0	0
Intent-to-Treat 1	0	0	Ō
Intent-to-Treat 2	0	0	0

^{*} Patients may be counted more than once. Reviewer's table

Country and Center Analysis- RH/E28

Denmark - Center 1 Results - Soren Solgaard MD (principal investigator)

	Unfractionated	Desirudin	Total (number of
	heparin (number of	(number of	patients)
	patients)	patients)	
Randomized	14	15	29
Prophylaxis period completed	12	15	27
Discontinued prematurely	2 .	0	2 (6.9%)
Adverse Event *	1	0	1
Other reason	1	0	1
Efficacy Analysis			
Per-protocol	12 (85.7%)	14 (93.3%)	26 (89.7%)
Intent-to-Treat 1	12 (85.7%)	15	27
Intent-to-Treat 2	14	15	29
Excluded from PP and ITT	2	0	2
No phlebography	2	0	2
Excluded from PP only	0	1	1
Concomitant medication not allowed	0	1	1
Efficacy Results			
Per-protocol	1 (8 3%)	0	1
Intent-to-Treat 1	1 (8.3%)	0	1
Intent-to-Treat 2	1 (7.1%)	0	1

Reviewer's table

Denmark - Center 2 Results - Carsten Torholm MD PhD (principal investigator)

	Unfractionated heparin (number	Desirudin (number of	Total (number of patients)
	of patients)	patients)	
Randomized	15	17	32
Prophylaxis period completed	14	15	29
Discontinued prematurely	1	2	3
Death	0	0	0
Adverse Event	0	1	1
Other reason	1 (WC)	1 (PX)	2
Efficacy Analysis			
Per-protocol	12 (80.0%)	11 (64.7%)	23 (71.9%)
Intent-to-Treat 1	13 (86.7%)	11 (64.7%)	24 (75%)
Intent-to-Treat 2	15	17	32
Excluded from PP and ITT	2	5	7
Inadequate central reading	1	4	5
No operation	0	1	1
No phlebography	, 1	2	3
Excluded from PP only	1	0	1
Concomitant medication not allowed	1	0	1
Efficacy Results			
Per-protocol	3 (25%)	1 (9.1%)	4

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Intent-to-Treat 1	3 (23.1%)	1 (9.1%)	4
Intent-to-Treat 2	3 (20%)	1 (5.9%)	4

Reviewer's table

Denmark - Center 3 Results - Per Willie Jorgenson MD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	12	12	24 (100%)
Prophylaxis period completed	10	10	20 (83.3%)
Discontinued prematurely	2	2	4 (16.7%)
Death	0	C	0
Adverse Event	0	1	1 (4.2%)
Other reason	2 (PX, WC)	1 (WC)	3 (12.5%)
Efficacy Analysis			
Per-protocol	9 (75%)	8 (66.7%)	17 (70.8%)
Intent-to-Treat 1	9 (75%)	8 (66.7%)	17 (70.8%)
Intent-to-Treat 2	12	12	24
Excluded from PP and ITT	3	4	7
Inadequate central reading	1	2	3
No phlebography	2	2	4
Efficacy Results			
Per-protocol	2 (22.2%)	1 (12.5%)	3
Intent-to-Treat 1	2 (22.2%)	1 (12.5%)	3
Intent-to-Treat 2	2 (16.7%)	1 (8.3%)	3

Reviewer's table

Sweden - Center 1 Results - Bengt Eriksson MD PhD (principal investigator)

Sweden - Center i results - Dengt L			
	Unfractionated	Desirudin	Total (number of
	heparin (number of	(number of	patients)
	patients)	patients)	
Randomized	21	22	43
Prophylaxis period completed	20 (95.2%)	19 (36.4%)	39 (90.7%)
Discontinued prematurely	1 (4.8%)	3 (13.6%)	4 (9.3%)
Death	0	0	0
Adverse Event	0	. 0	0
Other reason	1 (PX)	3 (AP, PX, WC)	4 (9.3%)
Efficacy Analysis			
Per-protocol	19 (90.5%)	17 (77.3%)	36 (83.7%)
intent-to-Treat 1	20 (95.2%)	18 (31.8%)	38 (88.4%)
Intent-to-Treat 2	21	22	43
Excluded from PP and ITT	1	4	5
Inadequate central reading	1	0	1
No phlebography	1	4	5
Excluded from PP only	1	1	2
Concomitant medication not allowed	1	0	1
Phlebography at wrong time	0	1	1
Efficacy Results			•
Per-protocol	5 (26.3%)	2 (11.8%)	7
Intent-to-Treat 1	6 (30%)	2 (11.1%)	8
Intent-to-Treat 2	6 (28.6%)	2 (9.1%)	8

Reviewer's table

Sweden- Center 2 Results - Lennart Ahnfelt MD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	28	30	58
Prophylaxis period completed	26 (92.9%)	28 (93.3%)	54 (93.1%)
Discontinued prematurely	2 (7.1%)	2 (6.7%)	4 (6.9%)
Death	0	0	0
Adverse Event	1	2	3 (5.2%)
Other reason	1 (PX)	0	1 (1.7%)
Efficacy Analysis			
Per-protocol	22 (78.6%)	24 (80%)	46 (79.3%)
Intent-to-Treat 1	22 (78.6%)	25 (83.3%)	47 (81%)
intent-to-Treat 2	28	30	58
Excluded from PP and ITT	6	5	11
Inadequate central reading	2	2	4

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No phlebography	4	3	7
Excluded from PP only	0	1	1
Phlebography at wrong time	0	1	1
Efficacy Results			
Per-protocoi	6 (27.3%)	0	6
Intent-to-Treat 1	6 (27.3%)	0	6
Intent-to-Treat 2	6 (21.4%)	0	6

Reviewer's table

Sweden - Center 3 Results - Claes Rothelius MD (principal investigator)

	Unfractionated	Desirudin	Total (number of
	heparin (number of	(number of	patients)
	patients)	patients)	
Randomized	25	24	49
Prophylaxis period completed	21 (84%)	19 (79.2%)	40 (81.6%)
Discontinued prematurely	4 (16%)	5 (20.8%)	9 (18.4%)
Death	0	0	0
Adverse Event	4	1	5 (10.2%)
Other reason	0	4 (3 PX, WC)	4 (8.2%)
Efficacy Analysis			
Per-protocol	18 (72%)	16 (66.7%)	34 (69.2%)
Intent-to-Treat 1	19 (76%)	17 (70.8%)	36 (73.5%)
Intent-to-Treat 2	25	24	49
Excluded from PP and ITT	6	8	14
Concomitant medication not allowed	0	1	1
Inadequate central reading	0	2	2
No phlebography performed	6	5	11
Excluded from PP only	1	1	2
Concomitant medication not allowed	1	1	2
Efficacy Results			
Per-protocol /	2 (11.1%)	4 (25%)	6
Intent-to-Treat 1	2 (10.5%)	4 (23.5%)	6
Intent-to-Treat 2	2 (8%)	4 (16.7%)	6

Reviewer's table

Sweden - Center 4 Results - Per-Olof Kroon MD PhD (principal investigator)

	Unfractionated	Desirudin	Total (number of
	heparin (number of	(number of	patients)
	patients)	patients)	
Randomized	21	21	42
Prophylaxis period completed	18 (85.7%)	19 (90.5%)	37 (88.1%)
Discontinued prematurely	3 (14.3%)	2 (9.5%)	5 (11.9%)
Adverse Event	1	1	2 (4.8%)
Other reason	2 (PX, WC)	1 (PX)	3 (7.1%)
Efficacy Analysis			
Per-protocol	15 (71.4%)	17 (81%)	32 (76.2%)
Intent-to-Treat 1	15 (71.4%)	17 (81%)	32 (76.2%)
Intent-to-Treat 2	21	21	42
Excluded from PP and ITT	6	4	10
Inadequate central reading	0	1	1
No phlebography	6	3	9
Efficacy Results			
Per-protocol	8 (53.3%)	2 (11.8%)	10
Intent-to-Treat 1	8 (53.3%)	2 (11.8%)	10
Intent-to-Treat 2	8 (38.1%)	2 (9.5%)	10

Reviewer's table

Sweden - Center 5 Results - Sven Biorkstrom MD (principal investigator)

	Unfractionated heparin (number of patients)	Des rudin (number of patients)	Total (number of patients)
Randomized	20	18	38
Prophylaxis period completed	18 (90%)	18	36 (94.7%)
Discontinued prematurely	2 (10%)	0	2 (5.3%)
Adverse Event	1	0	1 (2.6%)
Other reason	1 (PX)	0	1 (2.6%)
Efficacy Analysis			
Per-protocol	18 (90%)	12 (66.7%)	30 (78.9%)
Intent-to-Treat 1	18 (90%)	14 (77.8%)	32 (84.2%)

Intent-to-Treat 2	20	18	38
Excluded from PP and ITT	2	4	6
Inadequate central reading	0	3	3
No phlebography	2	1	3
Excluded from PP only	0	2	2
Concomitant medication not allowed	0	2	2
Efficacy Results			
Per-protocol	5 (27.7%)	0	5
Intent-to-Treat 1	5 (27.7%)	0	5
Intent-to-Treat 2	5 (20%)	0	5

Reviewer's table

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Sweden - Center 6 Results - Ralph Berg MD (principal investigator)

	Unfractionated	Desirudin (number	Total (number of
	heparin (number of	of patients)	patients)
	patients)		
Randomized	26	27	53
Prophylaxis period completed	23 (88.5%)	23 (85.2%)	46 (86.4%)
Discontinued prematurely	3 (11.5%)	4 (14.8%)	7 (13.2%)
Adverse Event	1	2	3 (5.7%)
Other reason	2 (AP, PX)	2 (PX)	4 (7.5%)
Efficacy Analysis			
Per-protocol	22 (84.6%)	20 (74.1%)	42 (79.2%)
Intent-to-Treat 1	22 (84.6%)	20 (74.1%)	42 (79.2%)
Intent-to-Treat 2	26	27	53
Excluded from PP and ITT	4	7	11
Inadequate central reading	1	3	4
No phlebography	3	4	7
Efficacy Results			
Per-protocol	1 (4.5%)	2 (10%)	3
Intent-to-Treat 1	. 1 (3.8%)	2 (10%)	3
Intent-to-Treat 2	1 (3.8%)	2 (7.4%)	3

Reviewer's table

Sweden - Center 7 Results - Julius Soreff MD PhD (principal investigator)

	Unfractionated	Desirudin	Total (number of
	heparin (number of	(number of	patients)
	patients)	patien:s)	
Randomized	25	27	52
Prophylaxis period completed	20 (80%)	24 (88.9%)	44 (84.6%)
Discontinued prematurely	5 (20%)	3 (11.1%)	8 (15.4%)
Death	0	0	0
Adverse Event	2	1	3 (5.8%)
Other reason	3 (2 PX, WC)	2 (PX)	5 (9.6%)
Efficacy Analysis			
Per-protocol	20 (80%)	23 (85.2%)	43 (82.7%)
Intent-to-Treat 1	20 (80%)	23 (85.2%)	43 (82.7%)
Intent-to-Treat 2	25	27	52
Excluded from PP and ITT	5	4	9
Inadequate central reading	1	0	1
No operation	0	1	1
No phlebography	4	4	8
Phlebography at wrong time	1	0	1
Efficacy Results			
Per-protocol	6 (30%)	0	6
Intent-to-Treat 1	6 (30%)	0	6
Intent-to-Treat 2	6 (24%)	0	6

Reviewer's table

Sweden -- Center 8 Results - Bengt Ellene MD (principal investigator)

	Unfractionated heparin (number of patients)	Desirudin (number of patients)	Total (number of patients)
Randomized	13	12	25
Prophylaxis period completed	11 (84.6%)	12	23 (92%)
Discontinued prematurely	2 (15.4%)	C	2 (8%)
Adverse Event	2	С	2 (8%)
Other reason	0	C	0
Efficacy Analysis			

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Per-protocol	10 (76.9%)	12 (100%)	22 (88%)
Intent-to-Treat 1	10 (76.9%)	12 (100%)	22 (88%)
Intent-to-Treat 2	13	12	25
Excluded from PP and ITT	3	0	3
Inadequate central reading	1	0	1
No phlebography	2	0	2
Efficacy Results			
Per-protocol	2 (20%)	1 (8.3%)	3
Intent-to-Treat 1	2 (20%)	1 (8.3%)	3
Intent-to-Treat 2	2 (20%)	1 (8.3%)	3

Reviewer's table

Appendix 3

Safety Data for Study RH/E 23

SUPPLIES OF CLINICAL ADMERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT TUNKFLATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR MIGHLY PROBABLE RELATION TO TREATMENT.

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The piven figures ere: "Total", the number of patients with any adverse experience in this category, most closly related to treatment the number of patients recording at least once the sources experience.

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SUMMARY OF CLINICAL ADVERSE FFFECTS DURING THE PROPHYLACTIC TREATHENT PERIOD BY RELATION TO TREATMENT TUNKTLATED = NOT OR UNIXELY ARLATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT) TO ATACAT.

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	unre Fi	1et.	<u>[</u> *	al. X	wir.	let.	rel	∎ţ.	unre n	lņt.	rel R	ot.	NU C	¹≅t.	rel	₽ŧ.	ş۰	let.	rel	aţ.
CARDIOVASCULAR DISORDERS, GENERAL 701AL	24	5.2		1.4	12	4.2	5	1.8	16	5.8		2.9	16	5.7	•	1.4	58	5.2	21	1.4
HYPOTENSION		2.9		1.4	5	1.8	3	1.1		2.9	6	2.2	٩	1.4	2	3.7	25	2.2	15	1.
HYPERTENSION	3	1.1	į		4	3.4			5	1.0	1	0.4	11	3.9			23	2.1	1	0.
SYHCOPE	ı	0.4	į		2	0.7	2	0.7	2	0.7			1	0.4	2	0.7	۱	0.5	٠,	8.
HYPOTENSION POSTURAL	1	0.4	ĺ		1	i			, z	0.7	2	0.4	1	0.4	į		4	0.9	1	٥.
CARDIAC FAILURE	١,	0.4	İ		1 1	0.4			[į			l,	0.4	į		١,	0.5	į	

The given Tiguras are: "Total": the number of patients with any edverse experience in this category, most closive related to treatment of the total number of patients reporting at least once the edverse experience, in secret of the total number of patients explaints are also do not be adverse.

SUPPLARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATHENT PERIOD BY RELATION TO TREATHENT LUMRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT) (DATASET: RANDOMISED PATTENTS)

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	Do	so 50	000	IV	De	sa 16	ng		Do	30 15	MQ)		Do	ae 20	ng		١.		•	
	l	N = 2	277		١,	r = 26	3		N	= 27	7		×	= 28	2			N • 1	117	
BODY SYSTEM CLASSIFICATION ADVERSE EXPEPERIENCE (IMM PREFERRED TERM)	O. C.	let.	Ľ,	10t.	UNF	lat.	5	let.	o reduce	lat.	rel	at.	ş e	let.	rel n		D. GDL0	1 nt .		=ţ.
CENTRAL AND PERIPHERAL HERVOUS SYSTE TOTAL	5	1.8	3	1.1	12	4.2	,	0.4	١,	2.5	•	1.4	14	5.0	4	1.4	38	3.4	12	1.1
DIZZINESS	1	0.4	2	0.7	•	1.4	1	0.4	3	1.1	4	1.4	2	0.7	3	1.1	10	9.9	10	3.9
HEADACHE	1	8.9	ł		١٩	1.4	•		3	1.1	1	8.4	١	2.1	}		14	1.3	1	.1
PARALYSIS	1				1	0.4	•		1	0.4			2	0.7			١ ٠	0.4		
PARESTHESIA	2	8.7	•		1	9.4			i	1	ļ ļ		ļ		ŀ		3	8.3		
DYSPHONTA	1	9.4	•		1				i i				1	9.4	•		2	9.2	ļ	
MYPOESTHESIA	ı		!		1		1		1				5	8.7	•		2	1.2		
MUSCLE CONTRACTIONS INVOLUNTARY	ı		ļ		1		1		1	0.4			1	0.4	!		z	.z		
NEUROPATHY	ł		ļ		1	0.4	l		1	9.4	ļ		l		1		Z	8.2	l	
PARESTS			; ;	8.4	١		ļ		1				1	•.•	ļ		1	9.1	ı	0.1
CRANIAL INJURY NOS	ĺ		1		1		ļ		ì				1	0.4	;		1	0.1		
HYPOTUNIA	ŀ		İ		1	0.4	;		ı				1		1		1	0.1		
MIGRAINE	1	0.4	Ì		1		!		ł				1		;		1 2	•.1	i	
NEURALGIA	1		į		١,	8.4	ì		ł		t		1		1		į i	0.1	l	
SENSORY DISTURBANCE	l		!				!		Ι.				.l		! 1	0.4	1		. 1	6.1
GASTROINTESTINAL SYSTEM BISORDERS TOTAL	44	15.4	ï	3.	2 46	16.3	i	2.9	45	14.2	.	2.1	43	15.2	1 .	1.4	178	15.9	20	2.
MAUSFA	26	4.4		3 1.	s 2:	7.8	4	5 1.4	23	8.3	5	1.4	23	8.2	2	0.7	· ~	8.4	15	1.
AGGILING	111	4.0	1 :	ı o.	4 11	3.1	!	3 1.1	12	4.3	§ 1	0.4	10	3.5			44	3.9	! 5	0.4

The given tigures are: -'Total': the number of patients with any edwarse experience in this category, most closly related to treatment the mamber of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

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SUPPARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATHENT PERIOD BY RELATION TO TREATHENT INNELLATED = POSSIBLE, PROBABLE OR MIGHLY PROBABLE RELATION TO TREATHENT) OF TREATHENT OF THE PROPERTY O

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	Dos	• 50	00 IU		D	20 10	ng	D	se 1	5 mg	Do	30 20) ag	7 '			
BODY SYSTEM CLASSIFICATION		= 2	77		,	× 28	3	!	1 = 2	77	×	- 21	D2	1	N = 1	1119	
ADVERSE EXPEPERIENCE (IN) PREFERRED TERM)	unrel	۳ŧ٠;		ţ.	25.0	let.	relat.	unre	ıınt.	rolet.	unre	iet.	relut.			re1	eţ.
WANTER FALELCATEURE (THM LAFLEKKED INVIT)	<u>-</u> -	<u></u> ¦		_	! —	<u></u>	<u> </u>	 "- -	<u>~</u> _	"	 "	<u> </u>	-" -	<u> </u>	<u> </u>	<u> </u>	<u>,</u>
GASTROINTESTINAL SYSTEM DISORDERS CONSTIPATION		2.9			,	3.2			2.9			2.1		31	2.8		
DYSPEPSIA	5	1.8			6	2.1		1	0.4	•	3	1.1	:	15	1.3	į	
PAIN ABDONINAL	4	1.4			2	9.7		۰	1.4	ĺ	5	1.8	Ì	15	1.3	į	
DIARRHEA	3	1.1	2	0.7	۰	1.4		۱۹	1.4	1	ı	0.4	•	12	1.1	2	9.2
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HOUTH DRY	3	1.1	}		1		i	1 2	0.4	!	ļ		ļ	١٠	0.4	Ì	
AMOREXIA	2	0.7			ĺ		<u> </u>	1		1	l		•	2	8.2	į	
ESOPHAGITIS .		1	1		1	0.4	}	l		1 0.4	l		1	1	9.1	1	0.1
FLATULENCE	1	0.4	1	0.4	l		¦	1		1	1		1	1	0.1	1	0.1
MEHORRHOTOS)	ļ	}				!] 2	0.7	}	1		}	, 2	6.2	4	
ABDOMEN ENLARGED	l	1	ł		l		•	1	8.4	}	1		1	1 1	9.1	ľ	
CASTROINTESTIMAL DISORDER NOS	1	1	}		1	0.4	1	1		1	l		ļ	1	0.1	1	
GT HEMORRHAGE	1	0.4	}		1		ļ	1		}	1		-	1	0.1	1	
HEHDRRHAGE RECTUM	1	!	1	0.4			1	1		1	1		1			1	0.1
неноявногоз тиконвозер	1	1	1	0.4			İ	l		1			į	1		,	0.1
HERHIA HIATAL	1	0.4	į				į	ł		!	1		į	,	0.1	į	

The given figures are: "'Total': the number of patients with any adverse experience in this category, most closiv related to treatment the number of patients reporting at least once the adverse experience.

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT (UNRELATED = MOY OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT) IDATASET: RANDOWISED PATIENTS

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	Do	so 50	oo tu	Do	** 10) g		Do	so I.	r-g		Do	na 2	0 mg		Ι'	0 1		
BODY SYSTEM CLASSIFICATION	1	N = 2	77	×	= 28	3		N	= 27	7		₩	= 2	82		ŀ	W = 3	119	
ADVERSE EXPERENSENCE (IMN PREFERRED TERM)	S)re	let.	relet.	unre	1∎t. Ž	۲-,	ž.	Spre	tet.	rel r	∍ţ. ,	n n	ışt. X	rel	at.	D AUL	žt.	re) n	
GASTROINTESTINAL SYSTEM DISORDERS HICCUP				1,	0.4											,	0.1		
ILEUS PARALYTIC	Ì			1								1	0.4	i			0.1	ĺ	
PEPTIC ULCER	1	0.4		1	i							l		į		1	8.1	ĺ	
PRURITUS ANI		Ì		1		İ		İ				1	0.4	į		1	0.1	ĺ	İ
STUMATITIS	l	Ì	i i	1		İ		· .		1	0.4	l		j		1		1	0.1
STOMATITIS ULCERATIVE	1		!	1	0.4	!		l		!		1		!		1	0.1	į	
MEART RATE AND RHYTHM DISORDERS TOTAL	7	2.5	}	5	1.8	; ;	0.4	5	1.3	· ī	9.4	٩	1.4	1	0.4	21	1.9	3	0.3
TACHYCARDIA	2	0.7		1	0.4	1	0.4	1	0.4	1		2	9.7	1		6	0.5	1	0.1
FIBRILLATION ATRIAL	2	0.7	1	1	0.4	:		Į.		ı	0.4	2	0.7	1		5	0.4	1	0.1
BRADYCARDÍA	2	0.7	!	2	0.7	!				1		1	0.4	1		5	0.4	İ	
ARRHYTHMIA	1	0.4	İ	ŀ		į		3	1.1	l		ŀ		•		١.	0.4	İ	
EXTRASYSTOLE VENTRICULAR			Ì	1	0.4	•				İ		1		Ì		1	0.1	İ	
EXTRASYSTOLES	l		İ	ı		Ì		1	0.4	İ				ĺ.		1	0.1	ĺ	
FIBRILLATION VENTRICULAR	l		!			!		1		•		1		1	0.4			1	0.1
HEMIC AND RETICULOENDOTHELIALIRESISY TOTAL	T		i			ī		1	0.4	i		Г		i		1	0.1		
NEMATOLOGICAL DISORDER	1		!	1		į		1	0.4	•		1		ļ		1	0.1	į	

The given figures are: "Total": the number of estients with any adverse experience in this category, most closic related to treatment

- the number of patients reporting at least once the adverse experience,
in percent of the total number of patients smallessed for early

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SUPPIARY OF CLIMICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT (UNRELATED = NOT) OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT) DATASET; RANDOMISED PATIENTS

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		B	se 5	000	tu	T	Dos	- 10	100	0	79e 15	-)	De	90 2	0 p	9] '	٠,	, ,	
BODY SYSTEM CLASSIFICATION			10 = :	277		L	24	= 28	3	1	N = 22	77		١,	. = 2	182			N = 1	1117	
ADVERSE EXPERENCE LIM PREFERRED	TERM)	500	ist.		101.	3,5	rel	at.	relet.	טארי	let.	3,3		UNIT O	let.	; ;	olot. X	upera	iet.	Lej	
LABORATORY ABHORMALITY	TOTAL	21	7.6	١,	. 0.	ء ا	1	7.4		22	7.9	,	2 9.7	26	9.2	2		90	8.0	3	0.
HYPOKAL ENTA		17	6.9	,	0.	۱ ۱	.9	6.7	l	22	7.9	1		24	8.5	ş İ		84	7.5	1	0.
CLYCOSURIA		1	6.4	į		1	ı	8,4		1				1		ì		2	0.2	į	
HYPERGLYCENIA		1	0.4	Í		1	1	0.4	•	1		ŀ		ı		į		2	6.2	İ	
HYPERKALEHIA		1		İ		1			ŀ	1		Ì		1	0.4	١Ĺ		1	9.1	ĺ	
HYPOCALCENIA				į		1			1	1			1 0.4	1		į				ļı	٥.
HYPOHAGNESEMIA		1		į		1	1	0,4	į	1		Ì		1		į		1	9.1	Ì	
LAB ABM - CLINICAL CHEMISTRY		1		Ĺ					į	1		į		1	0.4	٠į		1	0,1	ĺ	
LIVER ENZYMES ELEVATED		}		į		1			į	1		•	1 0.4	·I		į		Ì		1	٥.
HETABOLIC AND MUTRITIONAL DISORDERS	TOTAL	1	0.4	;		Т	1	0.4	i	1 2	0.7	;		3	1.	1;	2 0.	7	8.6	2	٠.
HYPOVOLEHIA		1		i			1	0,4		1		1		į .		į	2 0.3	, 1	9.1	2	٥.
COUT .		1		į		1			į	۱ ا	0.4	ĺ		١,	0.	٩į		2	0.2	į	
MYPONATREMIA)		į		1			į	1,	0.4	İ		1	0.	٠į		1 2	0.2	į	
GLUCOSE TOLERANCE ABNORMAL		1	0.4	į		1			-	1		Ì		1		İ		1 1	0.1	i	
HYPERURICEHIA)		į		1			į	1		į		١,	٥.	٠į		١,	0.1	į	

The given figures are: "Total": the number of patients with any adverse experience in this category, most closiv related to treatmen
the number of patients reporting at least once the adverse experience,

SUPPLARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT GUARGLATED B NOT OR UNITATELY RELATED. RELATED B POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT.

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	Do	so 5	000 IU	Do	so 10	3 39		Do	se 15	mg		Do	se 2) ng		1 7	0 7	A L	
BODY SYSTEM CLASSIFICATION		H > :	277	N 1	2 21	3		H	= 27	17		×	= 2	82		ļ	H - 1	113	
ADVERSE EXPEPERIENCE (IMM PREFERRED TERM)	nure	lat.	relet.	unro	ì≱t.	, Le)	-ţ.	250	int.	re'i	• t .	متده	ıət.	Ľ.	-3.	UN.	101.	rel n	ut.
MUSCULOSKELETAL SYSTEM DISORDERS TOTAL	16	5.8		15	5.3	4	1.4	21	7.6	5	1.0	11	3.9	•	1.4	63	5.6	13	1.6
PAIN MUSCULO-SKELETAL	7	2.5	İ	a	2.8	3	1.1		2.9	2	0.7	3	1.1	3	1.1	26	2.3		0.7
JOINT DISLOCATION	2	0.7	į	1	0.4	į		6	2.Z	į		۱ 4	1.4	į		13	1.2		.
ARTHRALGIA	5	1.8	į	3	1.1	i		1	9.4			Į	0.7	į		11	1.0		
ARTHROSIS	١		į	1	8.4	ı	0.4	2	0,7	,	0.4	l		i		3			0.3
PAIN BACK	1		į	1		į		1	8.4	٠,	3.4	2	0.7	1	6.4	١,	0.3	,	
CRAMPS LEG	z	0.7	į	1		į		,	0.4	,	0.4	j		j		3		ì	0.
FRACTURE	lı	0.4	į	1	0.4	i		١,	3.4	ĺ		ĺ		•				_	
HYALGIA	1		į	1	0.4	į						١,	0.4	•		1	0.Z		
ARTHRITIS	1		į			•		١,	0.4			1		i		1		l	
BONE DISORDER	i		į			į		l.	0.4	į		1							
CRAMPS MUSCLE	1		į			ļ .		1	0.4	:		1		1		1 -	0.1		
HYO ENDO PERICARDIAL & VALVE DISORDE TOTAL	1		:	1.	2.1	: 1	0.4	1		-		1	0.4	. 2	0.7				G.:
ANGINA PECTORIS	1		į		1.4	:	0.4	Į .				1		:	•	1	0.4	,	
HYDCARDIAL INFARCTION	1		i	1	0.7	:						Ī		į,	0.4	1	0.2	! -	
HYOCARDIAL ISCHEMIA	1		į	1		į		1				l ·		١,	0.4	1 -		1	

The given figures are: "Total: the number of patients with any adverse experience in this category, most closiv related to treatment of number of patients reporting at least once the during experience, in parcent of the total number of patients analysed for safety

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SUPPLIARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT HURRELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT)

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BODY SYSTEM CLASSIFICATION	L		- 2			_		- 28	_		_	- 27			_	= 20				H = 1	1119	
ADVERSE EXPERENCE (INN PREFERRED TER			ž*.	70	int X			žt.	re-	let.	T. C.	201.		lai.	du.	191.		ież.	O.	191.	rei	-ş.
PLATELET, BLEEDING & CLOTTING DISORD TOTA	u 2	2	7.9	26	. 16	اء	24	8.5	47	16.6	21	7.6	65	23.5	21	7.4	63	22.3	58	7.9	221	19.
HEHORRHAGE NOS	2	25	7.9	37	13	.4	26	9.2	41	14.5	22	7.9	56	20.2	23	8.2	51	18.1	73	8.3	185	16.
иематома	1	2	0.7	15	5	.4	4	1.4	•	2.1	2	0.7	17	6.1	2	0.7	18	6.4	10	0.9	56	5.
COAGULATION DISORDER	┸		_ :	<u>!</u>				- 1	1	0.4	l		!		<u> </u>	!	<u>!</u>		[!	: 1	0.3
PSVCHIATRIC DISORDERS TOTAL	M 2	24	8.7				22	7.8	•	1.4	20	7.2	; 3	1.1	19	6.7	z	0.7	85	7.6	, ,	0.8
INSCIPITA	1	22	7.9				17	6.0	,	1.1	15	5.4	,	0.4	15	5.3	,	9.7	67	6.2		0.1
CONFUSION	-	1	0.4				1	6.4	1	0.4	3	1.1	1	0.4	2	0.7	}		7	8.6	łz	0.
AMRIETY	-			1			2	9.7	;		l l		; ;	6.4	1	8.4	l		3	0.3	1 2	ð.:
HALLUCINATION	1			:		1	3	1.1	ŀ		1		;		l		;		3	0.3	:	
AGETATION		1	0.4	•			l		;	0.4	·		;		ì				1	0.1	, 1	0.1
DEPRESSION	ł			•		į	1		ŀ		1		1	L 0.4	1	0.4	1		1 1	0.1	1	0.7
HERVOUSHESS	- 1						1	0.4	!		1		ļ		}		1		1	0.1	ļ	
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PERSONALITY DISORDER	1			ļ.			1		!		1	9.4	•		١.		ļ		1	9.1	İ	
RED BLOOD CELL DISORDERS 101	AL	74	8.7	ï	• :	3.2	17	6.0	j 1	. 5.	13	4.7	, 1	3 4.7	11	3.9	; 11	3.	65	5 b	j 47	4.
ANEMIA	- 1	24	8.7	!	• :	3.2	17	6.0	! 1	• •.•	13	4./	! 1	3 4.7	11	3.9	! 11	3.	65	5.8	. 47	4.

The given figures are: "Total": the marber of patients with any adverse superience in this category, most closicy related to transment the marber of patients reporting at least once the seprience,

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT (UMRELATED = NOT OR UNLIKELY MELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT) (DATASET: RANDOMISED PATTENTS)

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		Dо	se 50	00 1	שו	Do	10	ng		Dos	• 15	#0		Do	90 ZC	-9		•	٠.	~ .	
	- 1		N = 2	77		N	= 28	3	l	N	- 27	7	i	N	= 28	2			H = 1	119	
BODY SYSTEM CLASSIFICATION PREFERRED T			žt.	rei	at.	Vir.	12t.		ž.	UNF#	يود.	rei.	₽ŧ.	unre D	let.	Lo ₃	at.	ALL B	let.	rel	■ ‡.
REPRODUCTIVE DISURDERS, FEMALE	TOTAL	_				1	0.4		0.4									1	0.1	1	0.1
EDEMA GENITAL FEMALE	1					1	0.4				1	١.				}		ı	0.1	}	
VAGINAL HEMORRHAGE				į		Į .	į	1	0.4					l _		!				,	0.1
RESISTANCE MECHANISH DISORDERS	TOTAL	1	0.4	2	0.7	3	1.1	•	2.1	4	1.9	5	1.8	2	0.7	11	3.9	10	0.7	24	2.1
HEALING THPAIRED				2	0.7	1	1	5	1.8	1	0.4	5	5.1	1	0.4	33	3.9	2	0.2	23	2.1
INFECTION				ľ		l	ŀ	1	4.4	1	0.4	}		1	0.4	:		2	0.2	1	0.1
INFLUENZA-LIKE SYMPTOMS		3	0.4	•				}		1	0.4	ŀ		١		!		2	0.2	•	
HONILIASIS		l		1		3	0.4	}		1	8.4			1		}		5	6.2	1	
ABSCESS				ľ		1	0,4	ľ		ì		i		1		;		1	8.1		
INFECTION VIRAL				!		1	0.4	!		<u> </u>		!		<u>L</u>		!		1	0.1	<u>!</u>	
RESPIRATORY SYSTEM DISORDERS	TOTAL	10	3.6	i		15	5.3	3	1.1	10	3.6	4	1.4	13	9.6	1	0.4	48	4.3	j e	0.7
DYSPNEA		٠	1.9	1		3	1.1	1 3	1.1	١.	1.4	? 1		[2	0.7	1		13	1.2	3	0.3
COUGHING		3	1.1	1			1.4	ì		3	1.1	1		5	1.8	1		15	1.3	1	
BRONCHITIS		1		İ		2	0.7	ł		Z	0.7	1		. 3	9.4	1		5	9.4	,	
EPISTANIS		١.		İ		1		1		ì		} 4	1.4	1		1	0.4	·		5	0.0
PLEURAL FFFUSION		i		l		2	0.7	1		1	9.4	1		1	0.4	,		1 .	•.4	1	
BRONCHOSPASM		ļı	0.4	j		2	0.7	İ		1		1				;		3	0.3	1	
PHARYNCITIS		1		į		1	0.4	ļ		1	0.4	Į.		1 3	0.4	ı.		3	0.5	ı!	

The given figures are: "Total": the number of patients with any adverse experience in this estagery, most closiv related to treatmen the number of patients resorting at least once the adverse experience,

BEST POSSIBLE COPY

SURMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATHENT PERIOD BY RELATION TO TREATHENT INHRELATED = NOT OR URLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATHENT) LOATASET: RANDOWISSED PAILENTS.

CENTER: ALL

_	Unfractionated Heparin	}	CGP 39 393		
	Dose 5000 1U	Dose 10 mg	Dose 15 mg	Dose 29 mg	TOTAL
BODY SYSTEM CLASSIFICATION	H = 277	H = 283	H = 277	H = 282	N = 1119
ADVERSE EXPERENCE (I'M PREFERRED TERM)	unrelat. relet.	unrelat. relat.	unreset, relet.	unrelat. relat.	unrelat. relat
RESPIRATORY SYSTEM DISORDERS ASTHMA		1 0.4		1 0.4	2 0.2
BRADYFNEA	1	1	1 0.4	1 0.4	2 0.2
PULHUNARY INFILTRATION	1 0.4	1 0.4	1 1		2 0.2
APHEA	1	1	i	1 0.4	1 0.1
ASPIRATION	l i	1 0.4	1 1	1 1	1 0.1
INFECTION CHEST	1	1 0.4	1 1	1	1 0.1
PLEURISY		1 1		1 8.4	1 0.1
PHEURIUNIA		1 1	1 0.4	1 1	1 0.1
PHEURIONIA LOBAR	1	1 1		1 0.4	1 0.1
PHEURICHITIS	1 0.4	1 1	1 1	1 1	1 0.1
PULHONARY EDENA	1 1		1 1	1 0.4	1 0.1
RESPIRATORY DEPRESSION	1	1 0.4		1	1 0.1
RESPIRATORY DISORDER			1 0.4		1 0.1
RESPIRATORY INSUFFICIENCY	1			1 0.4	1 0.1
RHINITIS	1 0.4	1 !	!	i i	1 0.1

The given figures are: -'Total': the number of patients with any adverse experience in this category, most closely related to treatment
-the number of patients reporting at least once the adverse experience,

SUPPLARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATHENT PERIOD BY RELATION TO TREATHENT FUNRELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATHENT TO AMERICAN PROPERTY OF THE PR

CENTER: ALI

		rect.		bed					cc	P 59	393									
	Do	se 5	000	IV	P	050 1	0 mg		Do	se 15	ing		De	so 20) mg		T	0 7	A L	
BODY SYSTEM CLASSIFICATION ,	L	N = ;	277			N = 2	3		N	= 27	77		м	= 26	12			H = 1	119	
ADVERSE EXPERENCE (IIM PREFERRED TERM)	ner.	iet.	<u></u>	tet. Z	Sir	nat.	'n	at.	ş c	X X	70	eţ.	rist e	lat.	re)	oţ.	AL B	ışt.	[P	· ż
SKIN AND APPENDAGES DISORDERS TOTAL	11	4.0		7.	Γ.	2.)	11	3.9		2.9	,	2.5	3	1.1	15	5.3	28	2.5	•1	
PUPPURA	1		7	2.5	:		10	3.5	2	0.7	3	1.1				4.3		0.2		
BULLOUS ERUPTION	5	1.6	į		2	0.7	į		2	0.7	į	-	,	1.0			14	1.3		_
RASH	2	0.7	į		1	0.4	į		2	0.7	3	1.1	,	0.4	Í		١٠	0.5	3	
FLUSHING	2	0.7	1	0.4	·		į		١.		į		1	0.4			3	0.3	1	
RASH ERYTHENATOUS	2	0.7	ĺ		1 2	0.4	į		(1	0.4	ĺ		(,	0.4	_	
PRURITUS	1		ì		1		1	0.4	1	0.4	1	0.4	Ì		į		1	0.1	2	۰
URTICARIA	1		į		1	0.4	Ì		1	9.4	į		1		į		2	0.2		
DERHATITIS	ĺ		ĺ		1		į		ĺ		į		1	į	į į	0,4	1		ı	0
DERNATITIS CONTACT	1		Ì		١,	0.4	į		ł	į	į		1		į		1	0.1	1	
CCZEHA	ĺ		į		1	0.4	i		ĺ		į		1		į		1.	0.1	•	
HOT FLUSHES			Ì		i		į		l		į					0.4			١,	•
LIP DISORDER	1		į		1		į		1	0.4	į		ļ		į		١,	9.1		
RASH HACULOPAPULAR	1		į		1		į]		į		1.		į ,	0.4	1 -			•
RASH PUSTULAR	1	0.4	į				i		ĺ		Í		1		<u> </u>		•	0.1	ľ	
SKIN DISORDER	l		į		1				Į,	0.4			l		!		1;	0.1	ł	
SKIN DRY	l				١,	0.4	1		\	- • •	}		1		} '		١,	0.1	}	
SKIN ULCERATION	ı		ì		ł	0.4	:		i i		j		1		i		1:	0.1	•	

The given figures are: -'Total': the number of patients with any adverse experience in this category, most closely related to treatment the surges experience, in percent of the total number of patients analysed for enerty

(UMRELATED = NOT OR UMLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHEY PROBABLE RELATION TO (REATMENT)

CENTER:ALL

			ract toper		ted					C	CP 39	393									
		De	250 5	000	U	1)0 1e	10	ng	D	05 0 l	5 mg		De	30 20	mg		,	0 1	A L	
BODY SYSTEM CLASSIFICATION			H =	277			N =	26	3	Ŀ	M = 2	77		١,	1 = 26	2			H = 1	119	
ADVERSE EXPEPERTENCE (I'M PREFERRED TO	ERHI	unre n	iet.	ŗ.	let. Z	, L			relat. n %	Unr.	olet.		ot.	unre	1et.	re)	at.	m.	let.		•ţ.
SPECIAL SENSES OTHER, DISORDERS TO	OTAL			!		Π		-!				!-		Г		,	8.4			$\overline{}$	0.1
TASTE PERVERSION	- 1			į		1		į				<u>!</u>			- 1	1		1			0.1
URIHARY SYSTEM DISORDERS (DTAL	42	15.2	2	0.7	7 3	5 11	.7		38	13.7	; 3	1.1	26	9.2	4	1.9	139	12.4		0.1
URINARY RETENTION	- 1	33	11.9	İ		2	4 8	.5		24	0.7	1	0.4	21	7.4			•	9.1		0.2
URINARY TRACT INFECTION		6	2.2	lı	0.4	. I	5 1	.8	ĺ	3	1.1	į		l ı	D.4				1.3	-	
MEHATUREA		1	0.4	ļ	0.4	1		Ì		2	0.7	3	1.1	1	0.4	4	1.4	ı	0.4		0.
CYSTITIS		2	0.7	1			2 4	1.7		1	0.4	Ì		3	1.1			١.	9.7		
DYSURIA		2	9.7	ĺ		1		į	ĺ	2	3.7	İ		1	0.4	ĺ		5	0.4	ĺ	
OL IGURIA		1		1			2 4	1.7	!	3	1.1	Ì		1	į	į		,	9.4		
MICTURITION DISORDER		1	0.4	1		1	1 6	1.4	1	1		İ		,	0.4			3	0.3	i	
ANURIA				1		1		1	į	1	0.4	į		1	8.4			2	9.2		
PROCEDURE GENITO-URINARY				1					İ	1	0.4	, į		1	0.4			2	0.2		
BLADDER DISORDER	1	1		į		1		- 1	į	1		į		1	0.4			1	0.1	•	
RENAL FUNCTION ABNORMAL		ŀ		İ				į	i	1	0.4	į			1			1	0.1		
STRANGURY		1		į		1			İ	1	0.4	į						1			
URETHRAL DISORDER		Ì		į					ĺ	1	0.4	į		ſ	ì			١.	0.1	1	

The given figures are: -'Total': the number of patients with any adverse experience in this category, most closily related to treatment -the number of patients reporting at least once the edverse experience,

SURMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT TURBLATED = NOT OR UNIXELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION YO TREATMENT

CENTER: ALL

	Ī		rect! epor		ted					CG	P 39	393							0 т		
	1	Do	90 50	100 1	נט	D	90 1C	ng		Do	so 14	779		90	se 20			'	0 1		
MODY SYSTEM CLASSIFICATION			H = 2	277		Ŀ	7-25	3		N	= 27	7_		*	= 2 0	2		<u>'</u>	4 = 1 :	117	
ADVERSE EXPERENCE CITIL PREFERRED	TERM)	unte	int.	re	lut.	unr.	ışt.	rel	•ţ.	n n	101.	rel	ot.	air.	let.	rol	₽ţ.	unre:	1 9 1.	rel	aţ.
ASCULAR (EXTRACARDIAC) DISORDERS	TOYAL	14	5.1	35	12.6	1.	3.5	16	5.7	1,,	• . 3	12	4.3	4	1.4	14	5.0	40	3.4	77	6.9
THROMBOPMLEBITIS DEEP		12	4.3	29	10.5		3.2		5.2	1	4.0		2.9	1	1.1	10	3.5	35	3.1	59	5.
THROMBOPHLEBITIS		ĺ		2	0.7	ı	- 1.0		0.7	} _		1	8.4	1	- 1	,	0.7			,	0.4
EMBOLISH FULMONARY		1	0.4	,	1.1	١,	8.4	•		1		_		1	8-4	i -		,	0,3	. 3	0.
THRUMBOPHLEBITIS SUPERFICIAL		Ì		•		-		! .	0.4	1	į	2	9.7	ł			0.4	•		4	0.4
THROHBOSIS				; ,	0.4	.1		1	0.4	l		_		1		1	0.4	1	j	3	
CEREBROVASCULAR DISORDER		l		i		1				l i	0.4	i i	0.4	į .		į		١,	0.1	1	٥.
PAIN VEIN		1	9.4	į		ĺ		į		1		ĺ		1		ı	0.4	1	0.1	1	8.1
VISION DISORDERS	TOTAL	_		:		+		-		1	0.4	1	0.4	1	0.4	-		1 2	8.2	1	•
CONJUNCTIVITIS		1		į		1		i		١,	0.9	í -		1		ĺ		(,	0.1		
DIPLOPIA				i		1		į		1		1		١,	0.4	ļ		١.	0.1		
VISION ABNORMAL		1		•		1				i		1	0.4	1	•••	1		-		Ι,	٥.
MITE CELL SYSTEM DISORDERS	TOTAL			:- -		╁╌		: - -		۲,	0.9			-				1	0.1	<u>; </u>	<u>.</u>
LEUKOCYTOSIS		١		;				ŀ		1:	0.4	:		1		1		1:	0.1	:	

The given figures are: "Total": the number of patients with any adverse experience in this category, most closly related to treatment the number of patients reporting at least once the adverse experience,

Sponsor's tables volume 1.70 p.8-23-291-304

Safety Data for Study RH/E 25

CIPA: PROTOCOL ROVES

TABLE 9.3.22

SUPPLARY OF CLIMICAL ADVERSE EFFECTS BURDER THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT INVESTIGATION TREATMENT INVESTIGA

	enox:	-	In Do	'	46 wg	CGP	39393	Dose 1	5		7 0 7	AL	_
RANDONISED PATIENTS		*	- 10	36			N *	1043			H =	2079	
BODY SYSTEM CLASSIFICATION													
ADVERSE EXPERIENCE (IN PREFERRED TERM)	2			u Leji	eted X	un-	1eted	Le)	ated .	35	Inted Z	h-1	n ted
APPLICATION SITE PISORDERS TOTAL	7	٠.	1 9	,	0.68	•	. 0,30	25	2.40	٠	6.27	32	1.5
INJECTION SITE MASS				7	1.68	,	1.21	25	2.40	3	9.14	32	1.5
DIJECTION SITE PAIN	()	٥.	10			,	0.10			2	8.10		
DIJECTION SITE REACTION	١,	9.	10							1	0.05		
NODY AS A WHOLE - CEMERAL DISORDERS TOTAL	179	17.	28	49	4.73	202	19.57	47	4.51	381	10.33	76	4.6
HOUND SECRETION	40	4.	6 3	32	5.89	12	5.94	28	2.68	110	5.29	6.0	2.8
FEVER	94	5.	21			4	6.14	. 5	9.48	110	3.68	\$	8.2
EDEMA LEGS	27	2.	61	,	8.87	29	2.78	13	1.25	56	2.69	22	1.0
HYPERPYREXIA	31	2.	77			34	3.26	•		65	3.15		
PAIR	25	z.	14	3	4.29	19	1.82	. 2	8.29	-	2.12	5	9.2
PAIN CHEST	١.		39	2	0,19	1 12	1.13	•		16	0.77	2	0.1
MOUND PREHINDING	,		4.8	1	0.10	5	1.46	. 1	.10	10	9.48	z	0.1
edena peripheral			58	ı	0.10	3	9.21	,		٠,	0.43	1	0.0
HOUND DEHTSCHICE	١,		37	1	9.19	١.	0.36		9.10		8.38	2	0.1
ALLERGY	,		48				9.34	•		,	0.13		
COMPLICATION OF PROCEDURE	5		48			2	0.1	,		,	8,34		
HALAISE	١,					l			9.10	١,	8.10	1	0.0

CENTER:ALL

	enoxeparin Do	20 41 mg	CSP 39393	Down 15 mg	707	A L
RAMDOMISED PATIENTS	H = 10	36	н -	1845	N = 2	079
NODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)		related n %	unrolated n X	related n Z	unrolated h X	related n X
BODY AS A WHOLE - GENERAL DISORDERS ALLERGIC REACTION		1 0.10	1 0.10		1 0.05	1 0.0
PALLOR	2 0.19				2 0,10	
PROSTHESIS DISLOCATION	1 1.10		1 4.16		2 0,10	
ASTHENIA			}	1 9.10) U.O.
CYAHOSIS	1 0.10				1 0.05	
EDEMA	į		1 0.10		1 0.05	
EDEMA GENERALIZED	1 0.10				1 0.05	
EYELID EDENA	1 0.10		•		1 0.05	
DIFLUENZA L'IKE SYMPTONS	1 0.10		i		1 0.05	
INARY			1 0.10		1 0.05	
HALFUNCTION OF PROSTHESES AND HONOGRAFTS	1 8.20		l		2 0.05	
PAIN CHEST PRECONDIAL	1 8.10		ĺ		1 0.05	
PAIN CHEST SUBSTEINAL	1 0.10		1		1 0.05	
PERI-PROCEDURAL MEDICATION			1 0.10		1 0.05	
PHLYCTENOSIS			1 9.10		1 4.05	
RICORS.	1 0.10		l		1 0.05	

- 'Total' is the number of patients with any adverse experience in this category isset closly related to trial treats.)

- the number of patients reporting at least once the adverse experience, to the adverse of patients reporting at least once the adverse experience,

SIDMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATHENT PERIOD BY RELATION TO TREATHENT (SUMMELATED - NOT OR UNLIKELY BELATED, RELATED - POSSIBLE PROBABLE OR RECALL RELATION TO TREATHENT) (DAYSET REMOUNTS PATIENTS)

	-	34000		וע	Done	45	C	*	59593	Dose	25	-		7	0 7	AL	
RANDOMISED PATIENTS	T				1036				* -	1943					я -	2079	
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)	Ī		121	-	rei n	Loged	-		i eted		-1-	tod X	§e		ted	Ç**	leted
CARDIOVASCULAR DISORDERS, GENERAL 707	ա]։	208	30.	.42	4	0.39	1,	.0	21.51	10	•	0.96	228	10	.97	34	
HYPOTENSION	-	6 Z	3.	78	3	0.29	٠	7	7.30	•	,	9.84	139	•	.67	12	0.5
HYPERTERSTON	1	34	3.	20	1	0.10	1 3	1	2.97	3		0.10	65	3	.13	z	.1
SYNCOPE	-	7	9.	68			1	,	0.84				16	•	.77		
CIRCULATORY FAILURE	-	6	9.	.58			1	ı	0.10				7	•	. 34		
CARDIAC FAILURE	-	1	•.	.10			1	٠	0.36				5		.24		
HYPOTENSION POSTURAL	- }	z		.19			1	z	9.19				٠		.19		
PULITORIARY CONCESTION	1	2		19			1	1	0.10				3		.14		
BLOOD PRESSURE FLUCTUATION	ı	1		.10			1						1		.05		
MYPERTEXSION AGGRAVATED	- 1	1	•	.10			1						lı	•	. 05		

SLEPHARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT (UMERIATE) = ROSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT) (DAYASET: RAMONIZADE PATIENTS) CENTER: ALL

	enex	perin i	Dose	40 mg	CSP	37373	Dose 1	5 109		TOT	AL	
NAMOUNISED PATIENTS		H = 1	1036			н = :	1043			H = :	2474	
DODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (JIM PREFERRED TERM)		1eted	ŗė1	a tod	35.0	1eted	rel n	ated %	rance	lated X	, rel	a tod
CENTRAL, AUTOMONIC AND PERIPHERAL NERVOUS SYSTEM DISORDERS TOTAL	52	5.02	4	0.39	47	4.78	6	0.58	191	4.86	10	0.4
NE ADACHE	32	3.09			21	2.01	2	0.19	53	2.55	2	0.1
DIZZINESS	•	0.39	3	0.29		0.77	2	0.19	12	8.58	3	7.2
HIPGIONIA	_•	9.39			7	9.47			11	0.53		
PARESIS , .	3	9.29			•	9.38			7	9.34		
PARESTHESIA	2	0.17			1	0.15	2	9.17	3	0.24	2	0.1
CONVULSIONS	2	4.17			1	0.10			3	8.19		
MEUROLOGIC DISORDER MOS	1	0.10			z	8.19			,	0.14		
HYPERKENESIA	-1	8.IS			l	6.10			2	8.10		
HYPDESTHESIA			1	4.10	l		1	0.10	1		2	0.1
NEURALGIA	1	8.10			1	8.10			2	3.10		
HEUROPATHY	1 1	0.10			1	P.10			2	₹.10		
TREHOR	l				2	9.17			2	0.10		
CEREBROSPINAL FLUID ABHORNAL	1	0.10							1	0.05		
DYSPHUHIA	1	0.10			l				1	8.85		
HICRAINE	1	9.16			L				1	0.05		
GASTROINTESTINAL SYSTEM DISORDERS TOTAL	235	22.68	17	1.64	245	23.49	18	1.73	489	23.49	35	1.6

'Total' is the number of patients with any edverse experience in this enterpory (sost signify related to trial treate.)
the number of patients respecting at least once the adverse experience, in percent of the total number of patients snelysed for safety

SUPPLRY OF CLINICAL ADVERSE EFFECTS DURING THE TREAL TREATHENT PERIOD BY RELATION TO TREATMENT (UNRELATED = NOT OR UNRILELY RELATED = POSSIBLE, PRODABLE OR HIGHLY PROBABLE RELATION TO TREATMENT) IDATASET: RANDOMISED PATIENTS)

	enommerin D	10 pa 48 mg	CEP 39393 D	ose 15 mg	TOT	A L
NAMBONISED PATIENTS	ж - 1	1936	H = 1	943	N = 2	2079
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)	unrelated h X	releted N X	unrelated n X	releted n X	unrelated n Z	Lelejed
GASTROINTESTINAL SYSTEM DISORDERS HAUSEA	110 10.62	10 0.97	129 12.37	12 1.15	239 11.50	22 1.0
VONTTENG	71 4.85	5 0.48	79 6.73	3 8.29	141 4.78	8 9.3
CONSTIPATION	64 6.18		46 4.35	1 9.19	156 6.25	1 0.0
DIARDEA	23 2.22		24 2.30	2 0.19	47 Z.26	2 0.1
PATH ABDOMINAL .	9 0.87		10 0.96		19 0.91	
DYSPEPSIA	S 0.77	1 0,10	6 9.58	1 0.10	14 9.67	2 9.
HEMATEMESES	1 9.10	2 0.19		2 0.19	1 0.05	4 0.
CASTRITIS	3 0.29		1 0.10		4 1.39	
FLATVLENCE	1 9.19		2 0.19		3 0.14	
AMOREXIA	1		2 0.19		2 0.10	
GASTROINTESTIMAL DISORDER NOS	1 0.10		1 0.10		2 0.10	
ASSOCIATE DE LA RESERVA	j		1 0.10		1 0.05	
ANUS DISURDER			1 0.10		1 0.05	
DACCEMAL SECER			}	1 0.10	Į	1 0.
EDENA ORAL	1		1 0.10		1 0.05	
ENTERITIS .	1 0.10				1 0.05	
ENTEROCOLITIS	1 0.10		l .		1 8.05	

The given figures are : "Total" is the number of petients with any adverse experience in this category

the number of patients reporting at least once the adverse experience in percent of the total number of patients englysed for safety

SUPPLARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATHENT PERIOD BY RELATION TO TREATHENT (UNRELATED = POSSIBLE, PROBABLE OR MIGHLY PROBABLE RELATION TO TREATHENT) (DATASET: RANDOMISSED PATZENTS)

CENTER: ALL

/	enovaparin Dose 40 mg	COP 39393 Dose 15 mg	10741
RANDOMISED PATIENTS	N = 3036	H - 1843	H = 2079
BODY SYSTEM CLASSIFICATION AUVERSE EXPERIENCE (INM PREFERRED TERM)	unrelated related	unrolated related	userlated imlated
GASTROINTESTIMAL SYSTEM BISORDERS ESOPHAGITIS	1 0.10		1 0.05
FECAL INCONTINENCE	}	1 0.10	1 0.05
CASTRIC VICER	1 0.10	1	1 0.05
CASTRIC ULCEN PERFORATED	1	1 0.30	1 0.05
CINCIVAL PLEEDING	1 0.10	1	1 0.09
GL053ETTS	1 6.10		1 4.45
HEHDRIHOTOS	[1 0.10	1 0.05
ILEUS PARALYTIC	1 0.10		1 0.65
INTESTINAL OBSTRUCTION		1 0.10	2 0.05
MELENA		1 0.10	1 0.05
ORAL PAIN	1 0.10		1 0.05
PEPTIC ULCER HEHORIOMATC	}	1 6.10	1 0.05
RETLUX BANDEND-GASTRIC	1 0.10	1	1 0.45
STONATETES	}	1 9.18	1 0.05
TUMBLE STECOLORATION	. }	1 9.10	3 0.05
TOMOUE STRESTA	. 1 0.10	1	1 0.05
TOOTH ACHE	l l	1. 0.10	1 0.85

(most closly related to trie) treats.)

The number of patients with any edverse experience in this cated

The number of patients recording at least once the adverse experience.

SUPPLAY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATHENT PERIOD BY RELATION TO TREATHENT (UMRELATED = NOT OR UNICLELY RELATED, RELATED = POSSIBLE, PROBABLE OR MIGHLY PROBABLE RELATION TO TREATHENT) DRATECTE CRANCOCKED PATEDITS.

		enors	per in	Duna 4		CSP	19393	Do no 1	5 ~		707	A L	
AMOUNISED PATIENTS			N =	1934			16 = 1	1943			H = :	2077	
DODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INC. PREFERRED TERM)		unre	10ted	rila		Card o	leted Ž	rel n	a ted	ribe.	1 ptod	re1	a lad
HEARING AND VESTIBULAR DISUNDERS	TOTAL	4	0.39			5	0.48			,	0,43		
VERTIGO		3	0.29			5	8,48				1.58		
EAR ACHE		1	0.10			ļ.				1	0.05		
HEART RATE AND RIGHTIM DESORDERS	TOTAL	34	3.67	1	D. 10	35	3,34	1	0.10	73	3.51		0.1
BRASTCARDIA		16	1.54			17	1.63			33	1.57		
FIBRILLATION ATRIAL			9.58	1	0.10		0.77	1	0.10	14	8.67	2	0.10
TACHYCARDIA			0.77			5	0,48			13	8.45		
ARRHYTHELA		3	0.29			5	0.46				9.36		
EXTRASYSTOLE VENTRECULAR		1	9.10			1	9.10			2	0.15		
PALPETATEON	•	2	0.19			l				2	0.10		
ARRHYTHMEA ATREAL		1	9.10							1	0.05		
AV BLOCK		1	0.10			1				1	0.05		
BURDLE BRANCH BLOCK		l				lı	4.10			1	9.05		
CARDEAG ARREST		(1 1	0.10			1	0.05		
FIRSTLEATION CARDIAC		١,	0.14]				1	0.05		

"Total" is the number of patients with any adverse experience in this (most close) related to trial treats. I the number of patients reporting at least once the adverse experience, in percent of the total number of patients enalysed for safety.

SUPPLATY OF CLINICAL ADVERSE EFFECTS DURING THE TREAL TREATMENT PERIOD BY RELATION TO TREATMENT TUNKELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT; INVASCRIST PARDOMISSED PATIENTS.

CENTER: ALL

	enexe	per in	Dasa 40 mg	COP	39393	Dose 1	5 =9		707	AL	
RANDOMISED PATIENTS		и »	1034		H = :	1043			H = 2	2079	
BODY SYSTEM CLASSIFICATION / ADVERSE EXPERIENCE (I'M PREVERRED TERM)	Linca	leted	related	ale.	lated X	rel	et ad	up-	lated	rel n	eted X
INFECTIONS AND INFESTATIONS TOTAL	10	9.97		19	1.34	1	0.10	24	1.15		0.05
DESCTION	5	9.48		11	1.05	1	0.10	16	♦.77	1	9.05
DEFECTION VERAL	3	0.29		2	0.19			5	9.24		
REALTER STARTER				1	0.10			1	0.15		
MONILIASIS	1	0.18		l				1	0.05		
VAGINAL INFECTION NOS	a.	0.20							0.05		

SUPPLARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT INVESTIGATED - POSSIBLE, PROBABLE OR MIGHLY PROBABLE RELATION TO TREATMENT) IDATASET: RANGONISED PATIENTS

	enexa	perin	Done	46 mg	CGF	39373	Dosa 1	S =9		T 0 T	Al	
RAMDOMISED PATIENTS		N = 1	1934			H =	1043			m = 2	2079	
DODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (SHE PREFERRED TERM)	ran.e	1gted	rė)	atod Z	ξc	1gted	Lo ₁	ated	umre	leted Z	L.0.7	n tod
LABORATORY ASMORMALITY TOTAL	61	5.67	5	0.40	••	4.22	7	4.47	105	5.05	12	0.50
HYPOKALEHIA	48	4.63	1	0.10	33	3.16	1	0.19	#1	3.70	2	0.31
LAS ASM - CLEMECAL CHEMISTRY	5	0.48			2	8.19	2	8.17	7	0.34	2	9.14
LIVER ENCORES ELEVATED	3	0.27	3	1.27	1	9.10	1	9.18	•	0.19	•	4.19
HYPOPROTEINENIA	•	0.37				9.29			,	9.34		
GAMPIA-GT INCREASED	2	0.17			2	0.19			•	8.17		
LAB AIM - NEMATGLOGY	ı		1	0.10	1		2	0.19			\$	0.14
PHOSPHATASE ALKALIDIE INCREASED	3	0.29			l				3	8.14		
CALCIUM DEFICIENCY	1				1	0.10			1	9.95		
ESR INCHEASED	l				1	0,10			1	0.05		
NYFEROLYCERIA	Į	•			1	0.10			1	6.65		
MYTERRALERIA	1				1	0.10			1	0.05		
NYFOCALCENIA	1	0.10			1				1	8.05		
HYPOGLYCENIEA	1	0.10			1				1 1	0.05		
HYPOMAGNESEKIA	•				1	0.10			1	0.05		
PEUTEDARIA	1				1		1	0.10	4		1	0.0

SUPPAINT OF CLINICAL ADVERSE EFFECTS BURING THE TRIAL TREATMENT FERIOD BY RELATION TO IREATMENT (HOMELATED = MOT OR MURICILLY RELATED, RELATED = POSSIBLE, PROGRAME OR HIGHLY PROBABLE RELATION TO TREATMENT) (BATASET) RANDOMISED PATIENTS)

		er \ e)(a	perin (Dase	49 05	CEP	39393 (loss l	5 = 5		707	AL	
RANDOMISED PATIENTS			н -	1034			H = 1	1943			H = :	2079	
DODY SYSTEM CLASSIFICATION * ADVERSE EXPERIENCE (INN PREFERRID TERM)			lated 2		e tod X	ğe	leted Z	rel	nted Z		leted	rel n	oğod Ž
LIVER AND BILIARY SYSTEM DISORDERS	TOTAL	2	0.19	z	0.19	3	0.29	1	8.10	5	0.24	3	9.1
JAUROTCE		1	9.10			3	0.29			4	0.19		
HEPATIC FUNCTION ASMORMAL				2	9.19	1		1	0.10			3	0.1
CHULELITHIASIS		3.	0.10							1	0.05		
METABOLIC AND MUTRITIONAL DISORDERS	TOTAL	54	5.21	1	0.10	61	5.65			115	5.53	1	0.0
HYPOVOL SHILA		47	4.54	1	0.10	54	5.18			101	4.86	1	
HYPERURICEHIA		4	0.39			4	9.38				0.38		
ÇOUT		3	0.29			3	0.29			•	1.29		
HYPORATREHIA						2	0.19			2	0.10		
DEHYDRATION		1	0.10			ĺ				1	0.05		
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS	TOTAL	184	17.76	8	0.77	176	14.87	7	9.67	360	17.32	15	0.7
arthralgia		143	13.80	3	0.27	145	13.90	2	0.19	288	13.85	5	9.2
PAIN LEG		13	1.25	5	8.48	10	0.96	4	0.30	23	1.11	•	
JOINT DISLOCATION		12	1.16			5	9.48			17	9.82		
PAIN BACK		١.	0.58			10	0.96			16	0.77		
CRAMPS LED		١.	0.39			5	9.48				1.43		
ARTHROSIS			0.39			3	9.29			٦,	8.34		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category

the number of patients reporting at least once the adverse experience, in percent of the total number of patients analysed for safety

SUMMARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT (UMRELATED = NOT DR UMLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR MICHLY PROBABLE RELATION TO TREATMENT) (DATASET: RANDOMISED PATIENTS)

	enoxeperin Dose 40 mg	CGP 39393 Dose 15 mg	TOTAL
RAMBONISED PATIENTS	M = 1956	H = 1043	H = 2079
BUDY SYSTEM CLASSIFICATION	urrelated related	unrolated related	unrelated related
ADVERSE EXPERIENCE (IM PREFERRED TERM)	n X n X	n X n X	unrelated related
HUSCULOSKELETAL, COMMECTIVE TISSUE AND BOME DISORDERS CRAW'S MUSCLE	6 0.50	2 0.10	7 0.34
HYALGIA	2 4.19	2 0.19	4 0.19
BONE DISORDER	2 4.39		2 0.10
HYPERTONIA	2 0.19	[2 0.10
FRACTURE	1 0.10		1 0.05
HEHARTHROSES	i	1 9.10	1 0.05
INTERVENTEDRAL DISC DISORDER	<u> </u>	1 0.10	1 0.05
HUSCLE SPASHS	į.	1 0.10	1 9.05
MYDGELOSIS	1 0.10		1 0.05
OSTEONECROSIS	1 0.10	†	1 0.05
PAIN ARK	1 0.10		1 9.05
PAIN SKELETAL	1 0.10		1 0.05
TEMPRITIS	į	1 0.10 .	1 0.05
TORTICOLLIS	1	1 0.10	1 0.05

The given figures are : "Total" is the number of potients with any odverse experience in this cutegory (most clearly related to trial treats.)

- the number of extends respectively at least once the adverse experience.

		enexaper	in D)ose (40 mg	CCP	39393	lore l	5 🛶		TOT	A L	
RAMOOMISED PATIENTS		H	- 1	1934			N = :	1045			W = 1	2079	
DODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)		urrelat n 2	•4	Lor	eted X	Unive	12 gried	re!	sted Z	a.	leted Z	rel n	a tod
HYO ENDO PERICARDIAL & VALVE DISORDERS	TOTAL	0 6.	77	1	0.10	11	1.05			19	9.91	1	0.09
ANGINA PECTORIS		6 8.	58	1	0.10	,	9.86			15	0.72	1	0.8
HYOCARDIAL INFARCTION		2 9.	19			1	8.10			3	1.14		
CORGHARY ARTERY DISEASE NOS	•					1	0.10			1	9.65		
PLATELET, BLEEDING & CLOTTING DISORDER	PATOT	150 14	48	175	16.89	147	14.07	172	26.49	297	14.29	347	16.69
HEHORRHAGE HOS		144 13	.90	124	11.97	145	13.90	124	11.89	289	13.70	248	11.93
HEHATOMA		25 2	41	41	5.89	31	2.97	60	5.75	56	2.69	121	5.8
COAGULATION BISORDER		ĺ				1		2	0.19	1		2	0.1
THROHBOCYTHENTA		2 0	.19							2	0.10		
PROTHRUMBIN DECKEASED		l				1		1	0.10	1		1	0.0

The given figures are : 'Total' is the number of patients with any adverse experience in this category (most closly related to trial treets.)

- the number of patients reporting at least once the adverse experience, in percent of the total number of patients managed for safety

SURPHANY OF CLIMICAL ADVERSE EFFECTS DURING THE THALL TREATMENT FERIORS RELATION TO TREATMENT;

LUMREATED WORD ON UNLIMELY RELATED, RELATED POSSIBLE, PROBABLE ON HIGHLY PROBABLE RELATION TO TREATMENT;

LONG-SETT RESPONSES PATIENTS.

CENTER:ALL

			parin 1	Dose	40 200	CEP	39393	Dose 1	5 mg		TOT	AL	
RANDOMISED PATIENTS			N =	1036			N =	1043			H ±	2079	
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INM PREFERRED (ERM)		Unre	1 pled	Ľ.	eted X	unre	1sted	Les Les	nted X	w.r.	1pted	rei n	eted
PSYCHIATRIC DISORDERS T	OTAL	165	15.93	3	4.29	154	14.77			319	15.34	3	0.1
INSCHOLA	- 1	134	12.93			129	11.51			254	12.22		
AGITA FIGH	- 1	10	0.97			14	1.34			2%	1.15		
SLEEP DISORDER	ļ	11	1.06			15	1.25			2%	1.15		
CONFUSION	1	•	9.87	2	9.19	,	3.86			18	9.87	Z	8.10
MOCIETY	1	3	8.29	1	9.10	7	0.67			10	9.46	1	0.0
DEFRESSION		4	8.30			1	0.10			5	0.24		
HERVOUSHESS		1	.10			3	9.29			•	0.19		
DRUG ABUSE						1	0.10			1	0.05		
MALLUCIMATION	1	1	8.10			1				1	0.05		
PAMIC DISORDER		1	*.10			1				1	0.05		
PARONIRIA	i					1	0.10			1	0.05		
PSYCHIC DISORDER						1	9.18			1	0.05		
THINKING ABHORNAL						1	9.10			1	4.73		
RED BLOOD CELL DISORDERS	DTAL	81	7.52	45	4.34	72	6.90	43	4.12	153	7.36	88	4.2
amenta		78	7.53	35	3.36	72	6.78	32	3.07	150	7.22	67	3.2
HEMOCLOBIN DECREASED		3	1.29	10	0.97	l		11	1.05	3	0.14	21	1.0

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SIMPLARY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATHENT PERIOD BY RELATION TO TREATHENT (UNWELLATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO THEATHENT) (DATASET, RANDONISSED PATIENTS)

CENTER - M.L.

		enom	ntreq	Dose	40 mg	CGP	39393	Dose 1	5		T 0 T	A L	
RAMDOMISED PATIENTS			H =	1934			H = 1	1043			w = 2	1079	
BODY SYSTEM CLASSIFICATION			lated		ated		lated	1	eted		leted	1	eted
ADVERSE EXPERIENCE (INN PREFERRED TROS)		7		n .		7		'n	ž	6	7.	, n	
REPRODUCTIVE DISORDERS, FEMALE	TOTAL			1	0.10					l		1	5
VACENAL HEHORRHAGE				1	0.10							1	9.95
REPRODUCTIVE DISORDERS, MALE	TOTAL	1	6.10							1	0.05		
PHINOSIS		1	9,10							1	8.85	_	
RESISTANCE MECHANISM DISORDERS	TOTAL	1	1.10			3	1,29			•	1.17		
INFECTION FUNGAL		1	0.10			3	0.29			•	0.19		
RESPIRATORY SYSTEM DISORDERS	TOTAL	53	5.12	5	0.48	44	4.41	6	0.58	77	4.76	11	0.53
CONCRENG		15	1.45	1	0.10	13	1.25			28	1.35	1	0.05
DYSPHEA		15	1.45	1	9.10	11	1.05	Z	0.19	26	1.25	3	0.14
PHARYNGITIS		5	6.48			5	9.48			10	.48		
HYPOXIA		•	9.58			3	9.27			,	0.43		
RESPIRATORY DISORDER		1	0.10	1	0.10	3	0.29	Z	0.17	•	0.19	3	0.14
EPISTAXIS				2	0.19	2	9.17	2	4.17	2	0.10	•	8.19
PHEUMINIA		3	1.Z7			2	9.19			3	0.24		
BROHCHOSPASH		1	9.10			3	9.29			•	9.19		
PULMONARY EDEMA		Z	8.19			1		1	0.18	2	0.10	. 1	0.0S
RESPIRATORY DEPRESSION		2	0.19			1	9.14			3	0.14		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category [most closely related to trial treatm.]

SUPPLANT OF CLINICAL ADVENSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT (UNRELATED = NOT OR UMLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT) (DATASET: RAMOUNISED PATIENTS)

CENTER: ALL

	unoxuparin Dose 40 mg	CEP 39393 Done 15 mg	TOTAL
RANDOMISED PATIENTS	H = 1036	N = 1943	H = 2879
DOUY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INN PREFERRED TERM)	unrelated related	unrelated related	unrelated related
RESPIRATORY SYSTEM DISORDERS BRONCHISTS	1 0,10	1 0.10	2 •.1•
EDENA LARYIEK	1 9.19	2 0.20	2 0.19
PHINCTIS	2 9.19	1	2 0.10
APNEA	1 9.18	}	1 0.05
BRAUTPHEA	}	1 0.30	1 0.05
HYPOVENTILATION	1 0.10	i	1 9.05
THE CTION CHEST	1 0.10	1	1 0.05
DESTRUCTIVE AIRWAY DISEASE	1	1 0.10	1 0.05
RESPIRATORY INSUPPLICIENCY	1 0.10		1 0.05
SPUTUM INCREASED		1 0.10	1 0.05
YONSTLLITIS	1 0.10	1	1 0.05

The given figures are: - 'Total' is the number of patients with any adverse experience in this cate; next clearly related to trial treatm.)

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EMPHANY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT FERIOD DY RELATION TO TREATMENT INMICLATED = NOT OR UNITED TREATMENT OF

CENTER: AL L

	enar	tap	₩1n	Pose	40 =0	CSP	59373	Doss 1	5 mg		TOT	AL	
RANDONISED PATIENTS			H = 1	1936			N =	1943			N = 3	2079	
DODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (INM PREFERRED TERM)	\mathrew{v}_{n}	~1	nted X	Le)	eted Z	Unere n	anted X	rel n	N September 1	ğe	leted X	rel n	eted X
SKIN AND APPENDAGES DISCRUERS TOTAL	1 34	6	3.47	3	0.29	43	4.12	5	8.48	79	3.89		0.58
BULLOUS ERUPTION	1	,	0.87			5	0,48	1	8.10	14	0.67	3	1.05
PRINCITUS	1	7	0.68			5	1.48	5	8.17	12	8.58	ž	0.10
DERMATITIS CONTACT		5	0.48			6	0,77			13	0.63		
PRESSURE SORE	1 .	4	0.58			7	0.47			13	9.63		1
RASH	1 :	2	0.19	2	0.19	3	1.27			5	8.29	2	0.10
DERIMATITES	1			1	9.10	3	0,27	2	9.17	3	0.14	3	9.14
SKIN DISORDER	1					3	0.48			5	0.24		
ECZEMA	1 :	2	9.19			2	1.19			4	9.17		
SWEATING INCREASED	1	3	0.29			1	0.10			•	0.19		
FLUSHING	1	2	0.17			1	9.19			3	9.14		
RASH ERYTHEHATOUS	1	1	0.10			2	0.19			3	1.14		
URTICARIA	1	1	0.10			1		1	0.19	1	0.05	1	0.05
BRUISING	1	ı	0.10			l				1	0.05		
EDENA LIPS		1	0.10			1				2	8.05		
PSORTASIS	1					1	0.10				9.95		
SKIN ULCERATION	1	2	0.10			l				1	0.05		

The given figures are : - 'Total' is the number of patients with any adverse experience in this category

 the number of patients reporting at least once the adverse experience in percent of the total number of patients analysed for safety

SUPPLAY OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL THEATHENT PERIOD BY RELATION TO TREATHENT CHRECATED * NOT OR UNIXELY RELATED, RELATED * POSSIBLE, PROBABLE OR NIGHLY PROBABLE RELATION TO TREATHENT! CHARACTERS OF PAREDURING PATIENTS.

CENTER: ALI

		Ongota -	perin 1	Dose 4		CCP	39393 I	Dose 1	5 23		707	A [
RANDONISED PATIENTS			pt = :	2934			n - :	1943			H = 2	2079	
BODY SYSTEM CLASSIFICATION			3-4-4	7930	4-0		Inted		eted				
ADVERSE EXPERIENCE (IDM PREFERRED TERM)		n	19ted		7		- Z	<u> </u>		35	leted Z		ated X
SURGICAL AND HEDICAL PROCEDURES	10TAL	1	.10							1	0.05		
PROCEDURE BLOOD AND LYMPHATIC		1	0.10							_ 1	8.05		
URINARY SYSTEM DISONDERS	TOTAL	85	8.20	3	9.27	+3	4.92	•	0.38	178	8.54	7	1.34
URINARY RETENTION		45	4.34			44	4.22			89	4.20		
URINARY TRACT INFECTION		17	1.64			13	1.25			30	1.44		
OLIGURIA			0.77			10	1.96			18	W.87		
CYSTITIS		3	8,48			10	9.96			15	0.72		
Henaturia		3	0.29	3	8.29	2	9.19	3	1.29	5	9.24		0.29
BLADDER DISORDER		1	8.10			5	3.48				1.29		
HICTURITION DISORDER		3	0.29			2	0.19			5	8.24		
AMURIA		1	0.10			1	9.16	1	8.15	2	0.10	1	9.0
DESTRUCTIVE UROPATHY		1				2	0.19			2	0.10		
REMAL FUNCTION ADMONHAL		1				Z	0.17	•		2	0.10		
UNDWAY DICONTRIBUCE		1	0.10			1	0.10			2	0.10		
BACTERIURIA HOS		1	9.10			}				1	3.95		
DYSURIA		1				1	9.10			1	0.95		
MEHATURIA TRAUMATIC	•	1	0.10			1				1	8.05		

The given figures ere : - 'Total' is the number of petients with any edverse experience in this categor (seet clear) related to trial freeze...'
- the number of petients reporting at least once the edverse experience,

SUPPLIES OF CLINICAL ADVERSE EFFECTS DURING THE TRIAL TREATMENT PERIOD BY RELATION TO TREATMENT (UMRELATED = NOT OR UMLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT) IDATASET: RANDOMISED PATIENTS)

	enoxa	perin	Dose	48 ag	CUP	39393)ese 1	5>		701	A L	
RAMDOMISED PATZENTS		N = :	1036			H = ;	1943			N - :	2079	
BODY SYSTEM CLASSIFICATION ADVERSE EXPERIENCE (IDM PREFERRED TERM)	ribt.e	1ated	rė1	ated %		lated Z	rel n	ated X	a L	1sted X	rei n	ated X
URIMARY SYSTEM DISORDERS MICTURITION PREQUENCY	1	6.10							,	0.05		
MICTURITION UNGENCY					1	0.10			1	0.05		
PAIN URINARY TRACT	1	*.10			1				1	1.15		
PYLIKIA	i				1	0.10			3	0.85		
STRANGURY	ļ				1	9.18			1	9.05		
URDIARY TRACT DESCRIBER	1	0.10			ŀ				1	0.05		
VASCULAR (EXTRACARDIAC) DISORDERS TOTAL	31	2.99	41	3.96	28	2.60	35	3.36	59	2.84	74	3.66
THRORBOPHLEBITIS DEEP	20	1.73	26	1.93	20	1.92	12	1.15	48	1.92	32	1.54
THOUGHDOSIS	2	0.19	16	1.54	1	0.10	18	1.73	3	1.14	34	1.64
THROUGHT EBITIS	6	0.58	3	0.29	3	8.27	1	0.10	,	0.43	4	0.19
CEREBROVASCIRAR DISORDER			1	1.19	1	0.10	3	0.29	1	0.05	4	0.1
THROUGOFILEDITIS SUPERFICIAL	2	0.17	1	. 8,10	1	0.10			3	0.14	1	3.0
ENBOLISH PULNOHARY	l		1	0.10	1	9.16	1	2.10	1	8.05	2	#.1t
PHLEDITIS	1	0.10			l				1	0.05		
THROPBOERBOLISH					1	8.10			1	0,05		
THROHBOPHLEBITIS ARM					۱ ،	.10			1	D. 05		

SIPHARY OF CLINICAL ADVERSE EFFECTS DURING THE IRIAL TREATMENT PERIOD BY RELATION TO TREATMENT (UMRELATED = NOT OR UMLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT) IDATASET: RAMBONISED PATIENTS)

CENTER: ALL

		anexa	parin i	3090 41 Pg	CEP	39393 0	2000 1	5 mg		707	A L	
RANDONISED PATIENTS		H = 1636				H = 1843				N = 2979		
BODY SYSTEM CLASSIFICATION		1000	leted	related	ummi	lated	rel	- t-d	unre	lated	cel	befe
* ADVENSE EXPERIENCE (INN PREFERRED TERM)				nΣ			n	X	n	χ'	^	ž
VISION DISORDERS	TOTAL	3	1.27		•	8.38	1	0.10	7	0.34	1	9.85
CONJUNCTIVITIS		2	8.17		1	4.10			3	0.14		
CONJUNCTIVAL HEMORINIAGE		1	0.10				1	9.30	1	0.05	1	6.05
EYE COMPLAINTS		(3	0.19			1	0.05		
EYE DISORDER HOS		(1	0.10		i	1	0.05		
KERATITIS					1	9.19			1	0.05		
MILTE CELL SYSTEM DISORDERS	TOTAL	2	9.17		2	6.19			4	0.37		
LEUKOCYTOSIS		Z	0.19		1	0.10			3	0.14		
LEUKOPENÍA		}			,	9.19			1	0.05		

'Total' is the number of patients with smoot clealy related to trial treats.) the number of patients reporting at in in percent of the total number of pati

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Safety Data for Study RH/E 28

SUPPRAY OF CLIMICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT (LAMBELATED = NOT OR UNLIKELY PELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATMENT) IDATASET: RANGUMINED PATERNS!

CENTRE: ALL CENTRES

BODY SYSTEM CLASSIFICATION			Unfractionated Heparin Bose 5000 JU N = 220			CGP 39393 Doze 15 eg N = 225				T G T A L N = 445			
ADVERSE EXPEPERIENCE (LIN) PREFERRED TERM)		unrelet.		relat. n Z		ra.			₽ţ. Ž	unrelat. n %		Lej	at.
APPLICATION SITE BISORDERS	TOTAL	1	0.5	2	8.9			5	2.2	1	6.2	7	1.6
INJECTION SITE MASS		1	4.5	2	0.7			•	1.8	1	*.2	6	1.3
APPLICATION SITE REACTION		1				1		1	9.4	L		1	0.2
BODY AS A WHOLE - CENERAL DISORDERS	TOTAL	19	8.6	9	4.1	21	9.3	10	4.4	49	7.0	19	4.3
MOUND SECRETION		2	8,9	5	2.3	13	5.8	4	2.7	15	3.4	11	2.5
FEVER		,	4.1	3	1.4	5	2.2	3	1.3	14	3.1	6	1.3
EDEMA LEGS		3	1.4	1	0.5	3	1.3	1	8.4		1.3	2	0.4
PAIN CHEST		5	2.5			1		Z	0.7	5	1.1	2	8.4
RICORS		1	0.5			1	0.4			2	8.4		
AMAPHYLACTIC SHOCK		1	1.5			l				1	0.2		
CARDIOVASCULAR DISORDERS, GENERAL	TOTAL	1	1.8	1	0.5	11	4.9	3	1.3	15	3.4	4	0.5
HYPOTENSION			1.8			10	4.4	3	1.3	14	3.1	3	0.7
HYPERTENSION				1	0.5	1				1		1	0.2
SYNCOPE		1				1	0.4			1	9.2		

The given figures are: - 'Total' is the number of patients with any adverse experience in this category (nost closly related to trial - the number of patients reporting at least once the adverse experience,

SUPPLARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATHENT PERIOD BY RELATION TO TREATHENT JUNICLATED = NOT OR UNITIRELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATHENT DURINGST: RANDOMISED PATIENTS.

CENTRE: ALL CENTRES

BORY SYSTEM CLASSIFICATION	Unfractional Dose 5 N = 2	900 IU	CGP 343 Dose 15 H = 2	mg	Y O T A L N = 445			
ADVERSE EXPERIENCE (IN PREFERRED TERM)	umrelat.	relat.	umrelat.	miet.	umrelet.	relat.		
CENTRAL AND PERIPHERAL HERVOUS SYSTEM TOTAL	5 2.3	-	4 1.8		9 2,0			
DIZZIMESS	1 0.5	i	2 0,9		3 0.7			
NEUROPATHY	1 4.5		1 0.4		2 0,4			
PARESIS	1 0.5		1 0,4		2 0.4			
HEADACHE	1 0.5				1 0.2			
HYPOESTHESZA	1 0.5				1 0.2			
HEURALGRA	1 9.5				1 9.2			
ASTROINTESTINAL SYSTEM DISORDERS TOTAL	22 10.0	5 2.3	21 7.3	7 3.1	43 7.7	12 2.7		
HAUSEA	16 7.3	2 0.9	15 4.7	7 3.1	51 7.0	9 2.1		
VONETENG	4 1.0	j	3 1.3	1 0.4	7 3.6	1 4.2		
HEMATEMESIS	1 9.5	1 0.5	2 0.7		3 0.7	1 0.		
DIARRHEA	2 0.7	1 0.5	1		Z 0.4	1 0.2		
GASTROENTERITIS	2 9.9	j	1 0.4		3 0.7			
CONSTIPATION	1 0.5		1 0.4		2 0.4			
PAIN ABDOMINAL	1 0.5		1 9.4		2 0.4			
GASTRIC ULCER PERFORATED	{	1 0.5	ı		l	1 0.2		
CASTRITIS	}	j	1 0.4		3 0.2			
HICCUP		1	1 0.4	. '	1 0,2			

The given figures are: "Total" is the number of patients with any adverse experience in this category (most closely related to trial the member of patients reporting at last once the adverse experience, in section to the total member of patients analysed for safety

BODY SYSTEM CLASSIFICATION ADVERSE EXPERATENCE (ZMM PREFERRED TERM)		Untra	ctions Dose 5	DOD IU	meri n	CCP 39393 Dose 15 mg N • 225				T O T A L N = 445			
			unrolet.		relat.		unrelat.		ţ.	oprolet.		relet.	
HEART RATE AND RHYTHM DESCRIBERS	TOTAL	3	1.4				2.8,			,	1.6		
BRADYCARDIA		Z	0.9			2	9.9			•	9.9		
FIBRILLATION ATRIAL		1	8.5			2				3	0.7		
TACHYCARDIA SUPRAVENTRICULAR		ł				2	0.4			1	0.2		
LABORATORY ABNORMALITY	TOTAL	1	0.5	3	1.4	5	8.9	1	0.4	3	0.7	4	0.4
LIVER ENZYMES ELÉVATED		ļ		2	9.9	l		1.	0.4	ļ		3	0.7
HYPOKALEHEA		}				2	0.9			2	1.9		
HYPOCALCENIA		1	0.5			į .				1	8.2		
PHOSPHATASE ALKALINE INCREASED		[1	0.5					ł		1	.2
LIVER AND BILIARY SYSTEM DISORDERS	TOTAL			1	0.5							1	9.2
HEPATOCELLULAR BAHAGE				1	0.5	1		_		1		1	6.2
METABOLIC AND MUTRITIONAL DISORDERS	TOTAL	1	0.5			2	0.9			3	9.7		
HYPOVOLEHIA		1	0.5			1	0.4			2	.4		
KETOSIS		1				1	0.4			1	0.2		

	Unfe	Dose 51		CGP 393 Dose 11	эд	7 0 T A L H = 445		
BOOV SYSTEM CLASSIFICATION ADVIRSE EXPERENCE (IPM PREFERRED TERM)	UNF	alet.	relet.	unrelat.	relet.	unrelat.	rolet.	
AUSCULOSKELETAL SYSTEM DISORDERS TOTAL	L 10	4,5	-	2 0.9	1 0.4	12 2.7	1 0.2	
JOINT DISLOCATION	•	1.8		2 0.9		6 1.5		
CHAMPS LEG	2	0.9		}	. 1 0.4	Z 4.4	1 0.2	
PATH BACK	2	0.9		l .		2 0.4		
ADMESIVE CAPSULITIS	1 1	0.5		ŀ		1 0.2		
ARTHRALGIA	- (2 0.4		1 0.2		
PAIM LEG	د {	9.5		}		1 0.2		
MYG ENDO PERICARDIAL & VALVE DISORDERS TOT	W 1	0.5	2 0.9	1 1.4		2 0.4	2 0.4	
ANGINA PECTORIS	1	0.5	2 8.9	ľ		1 0.2	2 0.4	
HYOCARDIAL INFARCTION)			1 9.4		1 0.2		
PLATELET, BLEEDING & CLOTTING DISORDER TOT	AL E	3.6	17 7.7	8 3.6	18 8.0	16 3.6	35 7.9	
HENORRIAGE HOS	1 7	7 3.2	12 5.5	5 2.2	12 5.3	12 2.7	24 5.4	
HENATONA	1	0.5	+ 4.1	4 1.8	10 4-4	5 1.1	19 4.3	
THROHBOCYTOPENIA	1		1 0.5	[1	1 0.2	

CENTRE: ALL CENTRES

OUV SYSTEM CLASSIFICATION			etiona Do sa S N = :	iii D			CEP 393 Doso 15 N = 2	-		T O T A L N = 445		
ADVERSE EXPERENCE (IN PREFERRED TERM)	rabba	ışt.	rel n	ŧ.	200	let.	relet.	Gree	ılmt. X	rel	ģ.
PSYCHIATRIC DISORDERS 1	OTAL	3	1.4	2	1.9	5	2.2	1 0.4		1.0	3	0.7
ANGLETY		1	0.5			3	1.3		٠,	8.9		
CONFUSION		2	8.9	1	4.5	1	1.4		3	0.7	1	0.Z
INSCINIA		Į				i		1 4.4	1		1	0.2
NERVOUSKESS						1	0.4		1	e.z		
PSYCHOSIS		l		1	9.5	1			1		1	0.2
REB BLOOD CELL DISORDERS 1	OTAL	 		- 2	1.7	-		3 1.3	7		5	1.1
AMERICA		1		2	8.9	}		3 1.3	1			1.1
REPRODUCTIVE DISORDERS, FEMALE 1	DTAL			1	0.5				_		1	0.2
UTERINE HEHDRRHAGE		i		1	9.5	1			1		1	0.2
REPRODUCTIVE DISORDERS, SEX UNSPECIFIE 1	OTAL	1	0.5						1	9.Z		
MONILIASIS CENITAL		1	0.5			i			1	0.2		_
RESISTANCE MECHANISM BESORDERS T	OTAL	6	2.7			3	1.3		,	2.0		
INFECTION		3	1.4			2	0.9		5	1.1		
HONILIASIS		3	1.4			1			3	9.7		
HERPES SIMPLEX		l l		•		١,	0.4		1	9.2		

SUPPLARY OF CLINICAL ADVERSE EFFECTS DURING INC PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT LUMBELATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR MIGHLY PROBABLE RELATION TO TREATMENT) LOATASET: RANDOWISED PATIENTS

CENTRE. ALL CENTRES

		Unfr	Dose 5			GP 393 Dose 15	i ng		7 O T	_	
BODY SYSTEM CLASSIFICATION ADVERSE EXPERENCE (IPM PREFERI	TENT)		olet.	relet.	ume		rolet. D Z	Latera	let.	rel n	
RESPIRATORY SYSTEM DISORDERS	TOTAL	,	3.2	1 0.5	6	2. 7	R 0.4	13	2.9	2	0.4
PHELPIONIA		1	0.5	1 0.5	2	0.9		3	0.7	2	0.2
DYSPNEA		1	0.5		2	0.9		3	0.7		
RESPIRATORY DEPRESSION		1	0.5		1	0.4		2	0.4		
ASTIMA		l			1	0.4		1	9.2		
BRONCHITIS		1 1	0.5				-	1	0.2		
BROHCHDSPASH	•	1	0.5					1	0.2		
CONCILING		1	4.5		•			1	1.2		
EPISTAXIS		!					1 0.4			1	Ø.2
PULHONARY EDEMA					1	0.4		1	0.2		
RHINITIS		1	0.5					1	8.2		

The given figures are: 'Total' is the number of patients with any adverse experience in this category twest closic related to trial the number of patients reporting at least once the adverse experience,

SUPMARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATHENT PERIOD BY RELATION TO TREATHENT LUNGLATED = NOT OR UNLIKELY RELATED, RELATED = POSSIBLE, PROBABLE OR HIGHLY PROBABLE RELATION TO TREATHENT) LOAFASET: RANDOMISED PATTENTS

CENTRE: ALL CENTRE

			octions Dose 5	• 1		CGP 393 Dose 15 N = 3	*9	T O T A L N = 445		
BODY SYSTEM CLASSIFICATION ADVERSE EXPERENCE (IMM PREFERRI	ED TERMI	Umr	ž.	reint. n X	UPP 0	lat. Ž	rwlet.	unrelat	, relat. n %	
SKIN AND APPENDAGES DISORDERS	TOTAL	۱ 4	1.8		11	4.9		15 3.	•	
URTICARIA		1 1	0.5		4	1.8		5 1,	1	
BULLOUS ERUPTION		1			2	0.9		2 0.	.4	
PRURITUS	•	}			2	0.9		2 .	4	
ACNE		İ			1	0.4		3 0.	2	
DEMIATITIS		1	0.5					10.	2	
DERMATITIS CONTACT		1	0.5					1 1.	2	
INFECTION SKIN		1			1	0.4		1 0.	2	
SEBORRHEA					1	0.4		1 0.	2	
SKIN ULCERATION		1	0.5		l		_	1 8.	2	
URINARY SYSTEM DISORDERS	TOTAL	10	4.5		21	9.3	3 1.3	33. 7.	.0 3 4.7	
CYSTITIS		5	2.3			3.6		13 2.	.•	
URINARY TRACT INFECTION		3	1.4		' 7	3.1	1 0.4	10 2.	2 1 8.2	
URINARY RETENTION		3	1.4	•	3	1.3	,	6 1.	3	
HEMATURIA		1	0.5		2	9.9	2 9.9	3 a.	7 2 4.4	
DLIGURIA		1			3	1.3		3 0.	.7	

The given figures are: - 'Total' is the number of patients with any adverse experience in this category (most closely related to trial - the number of patients reporting at least once the adverse experience,

SUPPLARY OF CLINICAL ADVERSE EFFECTS DURING THE PROPHYLACTIC TREATMENT PERIOD BY RELATION TO TREATMENT (UNRELATED = POSSIBLE, PROBABLE OR MIGHLY PROBABLE RELATION TO TREATMENT) TRATTERT (UNATASET: RAMOUNISED PATIENTS)

CENTRE: ALL CENTRES

BODY SYSTEM CLASSIFICATION	Unfractions Dose 5 N =		CGP 393 Boto 15 N = 3	5 mg	T O T A L H = 445			
	wrolst.	relet.	urelet.	relat.	urrelet.	relut.		
ADVERSE EXPERENCE (IN PREFERRED TERM)	n Z	n X	n 2	* X	7 7	n ż		
VASCULAR (EXTRACARDIAC) DISORDERS TOTAL	28 12.7	10 4.5	8 3.6	4 1.5	36 8.1	14 3.1		
THROMBOPHLEDITIS DEEP	27 12.3	10 4.5	8 3.6	4 1,8	35 7.9	14 3.1		
THROMBOPHLEDITIS	1 0.5				1 4.2			
VISION DISORDERS TOTAL	1 0,5				1 0.2			
INFECTION OCULAR	1 0.5		ł		2 0.2			

The given figures are : "Total" is the number of patients with any adverse aspariance in this entegory teest electly related to trial

the number of patients reporting at least once the adverse experience,

In percent of the total number of patients malysed for each of

Sponsor's tables volume 1.79 p.8-32-157-164

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Appendix 4

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Appendix 5- Materials Reviewed:

Materials - reviewed

Volume	Content
1.1	Overview of Application
1.48-1.69	Clinical Pharmacology Studies
1.70-91	Major Clinical Trials, including cardiology
1.92-124, SAS data sets	Case Report Tabulations
1.25-1.37	Case Report Forms

Reviewer's Table

Appendix 6- label



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Draft Labeling (not releasable)

Please see Dr. He's March 7, 2003 MOR for the Safety Update.

/S/

3-7.02

Alice Kacuba

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS MEDICAL OFFICER'S REVIEW

NDA: NDA 21-271/N-000-C

Sponsor: AVENTIS PHARMACEUTICAL PRODUCTS, INC

200 Crossing Boulevard

Bridgewater, NJ 08807-0890 USA

Drug name: Iprivask (desirudin)

Subject: An amendment to NDA 21-271 with a complete response to the

Approvable Letter dated May 14, 2001 and CMC Discipline

Review Letter dated April 16, 2001.

Date submitted: October 3, 2002

Date received: October 4, 2002

Review completed: March 4, 2003

Reviewer: Ruyi He, M.D.

1. EXECUTIVE SUMMARY

This submission is an amendment to NDA 21-271 with a complete response to the Approvable Letter dated May 14, 2001. The sponsor's responses are acceptable. The revised package insert should be further modified as recommended in section 9 (package insert review) below. Also, I recommend that the sponsor be requested to agree to a post-marketing commitment for further study in hepatically impaired patients to provide safety information and appropriate dosing regimen for those patients.

Overall, the safety information presented in the Safety Update Reports for the period between September 2000 and May 2002 is consistent with the known safety profile of desirudin. However, anaphylactic reaction was identified as a potential safety signal because of two case reports in cumulative experience. "Allergic reactions" is listed in the desirudin labeling under the section of PRECAUTIONS. "Anaphylactic/anaphylactoid reactions" is added in the section of ADVERSE REACTIONS, under the subsection of Post Marketing.

2. BACKGROUND:

NDA 21-271 was originally submitted on June 28, 2000 for desirudin. Desirudin (Iprivask, recombinant desulfatohirudin) is a selective thrombin inhibitor. Iprivask is proposed for the indication of the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery. For additional background information, see Medical Officer's Review dated May 11, 2001. The approvable letter for NDA 21-271 was issued on May 14, 2001 in which further CMC, pharmacology and clinical information were requested. Major clinical issues were as following:

- Address safety concerns regarding the proposed 2-count carton.
- Submit revised draft labeling
- Submit an alternate proposed proprietary name.
- Submit safety update

Although not required for approval, the sponsor also was requested to provide following information:

- Safety information from the first market date to the start of the Safety Update.
- Clinical information to support the labeling recommendations for switching from desirudin to other anticoagulants and from other anticoagulants to desirudin.

The letter also mentions that information provided in the NDA did not address use of desirudin in races other than Caucasian or provide safety information and optimal dosing regimen in hepatically impaired patients.

In this submission, the sponsor provides a complete response to the approvable letter and a proposed draft labeling.

3. SAFETY CONCERNS REGARDING THE PROPOSED 2-COUNT CARTON

The 2-count carton was labeled as ___ and the Division of Medication Errors considers that it may be mistaken that the total content of the 2-count carton is ___ of the active drug.

The sponsor proposed that the number — be changed to a bolded Two (2) so the content statement reads as follows:

"Two (2) x

Reviewer's comments: The sponsor's proposal is acceptable from a clinical standpoint. A consultation request was sent to the Division of Medication Errors regarding this issue and the review is pending.

4. ALTERNATE PROPOSED PROPRIETARY NAME

The sponsor submits the proposed proprietary name, IPRIVASK. The Division of Medication Errors has reviewed the proposed proprietary name and found proposed proprietary name, IPRIVASK is acceptable (see the consultation response from the Division of Medication Errors for NDA 21-271 dated December 5, 2002).

5. SAFETY UPDATE

5.1 Safety Update from September 2000 to November 2001

Desirudin is approved in 28 countries for the indication of prophylaxis of DVT in patients undergoing orthopedic surgery. So far, desirudin has not been withdrawn from the market anywhere, nor has its use been suspended anywhere.

Patient exposure

Cumulative worldwide patient exposure from the first quarter of 1999 to November 2001 shows an estimated absolute counting units of desirudin with 12,043 patients exposures. For the period of September 2000 to November 2001, there were approximately 6,448 patients exposures for absolute counting units.

Individual Case Histories

A total of 10 spontaneous reports were received between September 2000 and November 2001. Six of ten adverse events reported were serious and 3 of 10 (1 serious and 2 non-serious) adverse events were not listed before.

One serious and unexpected adverse event is violent abdominal pain requiring morphine sulfate. This was a 70-year-old female patient with no relevant history. She underwent knee surgery and received her first dose of desirudin SC pre-operatively. Post-operatively, she received a second desirudin injection, and 5 hours later, experienced violent abdominal pain requiring morphine sulfate. In the morning, she was found comatose and had developed hemorrhagic shock after 1300 cc blood loss from the surgical site. The patient recovered without sequelae.

Five serious listed adverse events are summarized below.

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Case #	Event	Causality	Outcome
200021292FR	Cutaneous erthematous and pruritus	Possible	Recovered
200021306FR	Hematuria, fever. Urinary cultures negative	Possible, ?	Recovered
200021491DE	73 yo F with plasmacytoma infiltrated to lung, bone marrow and kidney, increase in SGOT to 69, SGPT to 61, bilirubin normal	Possible	Ongoing
200110351FR	80 yo m with staphylococcal osteoarthritis developed pruriginous vesiculo-papular eruption	Possible	Recovered
200111089FR	Pulmonary embolism	Lack of effect	Recovered

Two adverse events which were listed as non-serious and unexpected were burning micturation, severe upper abdominal complaints and intestinal cramps.

Two other non-serious and expected adverse events were urticaria, generalized drug induced exanthema and difficulty in swallowing in the course of allergy.

5.2 Safety Update from November 2001 to May 2002

During the period November 2001 to May 2002, the worldwide sales of desirudin are estimated to be counting units. There were approximately 2,551 patients exposed.

During this period, only one spontaneous case (200213786DE) was reported. This case was a 62-year-old woman who experienced erythema, dyspnea and shock five minutes after her first subcutaneous dose of desirudin for thromboembolism prophylaxis. The reporting physician described the event as an anaphylactoid reaction and life-threatening. Her medical history was significant for heparin-induced thrombocytopenia and treatment with lepirudin in 1999.

A search of Aventis's Pharmacovigilance data base revealed one more report (DE01-05640) of allergic reaction. This was a 68 year-old man who experienced tachycardia. hypotension, chill and shock two to three minutes after his first dose of desirudin (15 mg) for thromboembolism prophylaxis.

In both cases, the temporal relationship between event onset and desirudin administration indicates desirudin might have caused the events.

No other adverse event was reported during this period.

5.3 Safety Update from May 2002 to September 2002

Two initial spontaneous reports of thrombocytopenia were reported in this period. In both cases, the patients had previous heparin-induced thrombocytopenia and were being treated concomitantly with heparin initially.

No other adverse event was reported during this period.

5.4 Conclusions of Safety Update

Overall, the safety information presented in these Safety Update Reports for the period between September 2000 and May 2002 is consistent with the known safety profile of desirudin. However, anaphylactic reaction was identified as a potential safety signal because of two cases reports in cumulative experience. Allergic reactions are listed in the desirudin labeling under the section of PRECAUTIONS. Anaphylactic/anaphylactoid reactions are added in the section of ADVERSE REACTIONS, under the subsection of Post Marketing.

According to the sponsor,

6. SAFETY INFORMATION FROM THE FIRST MARKET DATE (MALAYSIA-NOV 95) TO THE START OF THE SAFETY UPDATE (MAY 1, 99)

According to the sponsor, desirudin was

Germany was the first country where it was marketed on September 26, 1998.

There had been 5 adverse events reported in 3 patients, as of April 30, 1999. One patient experienced coagulation abnormalities, a second patient developed epistaxis and a third patient developed hemorrhagic shock secondary to an abdominal wall hematoma.

7. CLINICAL INFORMATION REGARDING SWITCHING BETWEEN DESIRUDIN AND OTHER ANTICOAGULANTS

In the approvable letter dated May 14, 2001, the sponsor was requested to provide clinical information to support the labeling recommendations on switching from oral anticoagulants to Iprivask or from Iprivask to oral anticoagulants, under PRECAUTIONS section, Drug interaction subsection. The sponsor was also requested to revise this paragraph to provide what is known and additional guidance how patients should be switched. In this submission, the sponsor has revised this subsection to read as follows:

Use in patients switching from oral anticoagulants to Iprivask or from Iprivask to oral anticoagulants.

The sponsor referred to a study (RH/E35) report in the original NDA 21-271 submission (6/28/00) to support above labeling recommendations for switching from desirudin to other anticoagulants and from other anticoagulants to desirudin. Study RH/E35 was an open label and single center trial to investigate the possible interaction between CGP 39 393 (rec-hirudin) and warfarin in 12 healthy male volunteers.

This study was a PK/PD study. According to the report, the co-administration of CGP 39 393 and warfarin was well tolerated by healthy volunteers. Bleeding times were comparable pre-dose, warfarin alone, CGP 39 393 alone and warfarin + CGP 39 393. APTT was prolonged for warfarin + CGP 39 393 compared to warfarin alone and PT was slightly prolonged for warfarin + CGP 39 393 compared to CGP 39 393 alone.

Based on the results of this PK/PD study, from a clinical standpoint, the above labeling recommendations are generally acceptable. However, because the oral anticoagulant used in the study was warfarin and oral anticoagulant activity was measured by INR, for greater clarity, I recommend the following modifications:

concomitation of warfarin did not significantly affect the pharmacokinetic effects desirudin. When warfarin and desirudin, were co-administration of hemostasis measured by activated part thromboplastin time (aPTT), prothrombin time (PT), and international normalizatio (INR) was observed. If a patient is switched from	of ed ial

8. OTHERS

In the Approvable Letter, the Division informed the sponsor that information provided in the NDA did not address the use in races other than Caucasian or provide safety information and optimal dosing regimen in hepatically impaired patients.

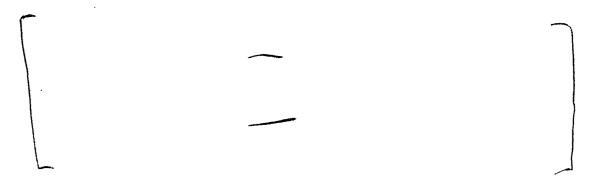
Regarding the use in races other than Caucasian, although in the clinical studies all of the patients were Caucasian, so far no reports or publications suggest that thrombin inhibitor may function differently between the races. Therefore, I consider that further study in different races is not necessary. However, the information about races of study subjects should be included in the CLINICAL TRIAL section of labeling (see section 9 below for detail).

Regarding the use in hepatically impaired patients, although Iprivask is not metabolized and eliminated in liver primarily, thrombin and many other coagulation factors are synthesized by liver. Safety information and information to direct dosing regimen in hepatically impaired patients are needed. Therefore, the sponsor should be requested to agree to a post-marketing commitment for further study (i.e., PK/PD study) in hepatically impaired patients to provide safety information and appropriate dosing regimen for those patients.

9. PACKAGE INSERT REVIEW

I have following recommendations for modifications of the package insert. The rationales will be provided with each recommendation. Otherwise, the revised package insert is acceptable from a clinical stand-point.

• Second paragraph in the section of CLINICAL TRIALS is proposed by the sponsor as following:



Reviewer's comments: The information about race, the numbers of patients enrolled, treated, and excluded from per-protocol population should be included in this paragraph. It is unnecessary to provide age and sex by treatment groups, because they were very similar in both groups. The sponsor declined to use "all

treatment population" for efficacy analysis as recommended by FDA, because the sponsor considered that it is not known whether non-evaluable patients had clinically occult VTE, the "all treatment analysis" may provide false low incidences of VTE. I recommend that this paragraph be modified as following. Additions are shown by the underline and deletions are shown by double-strikeout.

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patients were random	ized in the study	436 patients	were treate	d, and 85 p	atients wer	e
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years) with 41.8% m	nen and 58.2%	women. All	enrolled pa	tients were	: Caucasiar	n,
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Reviewer's comments: The information about race, the numbers of patients enrolled, treated, and excluded from per-protocol population should be included in this paragraph. It is unnecessary to provide age and sex by treatment groups, because they were very similar in both groups. The sponsor declined to use "all treatment population" for efficacy analysis as recommended by FDA, because the sponsor considered that it is not known whether non-evaluable patients had clinically occult VTE, the "all treatment analysis" may provide false low incidences of VTE. I recommend that this paragraph be modified as following. Additions are shown by the underline and deletions are shown by double-strikeout.

. A total of 2079 patients

eading of phle	efficacy analysis mainly because of no phlebography or inadequate
cading or pine	300g/up/17.
	Patients ranged in age from 18 to 90 years (mean age 68.5
zaara) with 41	.7% men and 58.5% women. All enrolled patients were Caucasian
(cais) with 41	.776 men and 38.376 women. An emoned patients were Caucasian.
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	ion of PRECAUTIONS, subsection of Antibodies/Re-exposure, the
sponsor propos	sed the following:
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	e-exposure: Antibodies have been reported in patients treated with
nirudins.	
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desirudin in Ph	nase III clinical trials.
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Reviewer's comments: The proposed labeling above is based on a PK/PD study in 12 healthy male volunteers. From a clinical stand-point, it is generally acceptable. However, because the oral anticoagulant used in the study was warfarin and oral anticoagulant activity was measured by INR, for greater clarity, I recommend the following modifications:

The —	
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desirudin. When warfarin	and desirudin, were co-administrated
greater inhibition of hemos	stasis measured by activated partial
thromboplastin time (aPTT), prothrombin tratio (INR) was observed. If a patient is sw to Iprivask therapy,	
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10. REGULATORY RECOMMENDATIONS

From a clinical standpoint, the sponsor's responses to the Division's approvable letter dated May 14, 2001 are acceptable. The revised package insert should be modified as recommended in section 9 (package insert review) of this review. Also, I recommend that the sponsor be requested to agree to a post-marketing commitment for further study (such as PK/PD study) in hepatically impaired patients to provide safety information and appropriate dosing regimen for those patients.

Ruyi He, M.D.

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HFD-180/Div. Files

HFD-180/R. Justice

HFD-180/J. Korvick

HFD-180/K.Robie-Suh

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HFD-180/S. Doddapaneni

HFD-180/L.Zhou

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f/t 03/07/03 rh

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NDA 21-271/N-000-C. RH

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Ruyi He 3/7/03 01:25:11 PM MEDICAL OFFICER

Kathy Robie-Suh 3/7/03 02:20:12 PM MEDICAL OFFICER Concur.

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